COR2ED

THE HEART OF MEDICAL EDUCATION

BREAST CANCER CONNECT
VIRTUAL EXPERTS KNOWLEDGE SHARE

NEW ORAL ENDOCRINE THERAPY OPTIONS IN BREAST CANCER

Tuesday 20TH JUNE 2023

DEVELOPED BY BREAST CANCER CONNECT

This programme is developed by BREAST CANCER CONNECT, an international group of experts in the field of breast cancer.

BREAST CANCER connect®
POWERED BY COR2ED

Acknowledgement and disclosures

This BREAST CANCER CONNECT programme is supported through an independent educational grant from Menarini Stemline Oncology. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

Expert Disclaimers:

- **Assoc. Prof. Aditya Bardia** has received financial support from Daiichi/AstraZeneca, Eli Lilly, Foundation Medicine, Genentech/Roche, Immunomedics/Gilead, Merck, Novartis, Pfizer, Phillips, Radius Health/Menarini, Spectrum Pharma, Taiho Pharm, Sanofi for consultant/advisory board and research grants, including institutional, from Daiichi/AstraZeneca, Genentech/Roche, Immunomedics/Gilead, Merck, Natera, Novartis, Pfizer, Radius Health, Sanofi.
- **Dr Sara Tolaney** has received institutional research funds from Genentech/Roche, Merck, Exelixis, Pfizer, Lilly, Novartis, Bristol Myers Squibb, Eisai, AstraZeneca, Gilead, NanoString Technologies, Gilead, Seattle Genetics, OncoPep and has received honoraria for consultant and advisory role from Novartis, Pfizer, Merck, Eli Lilly, AstraZeneca, Genentech/Roche, Eisai, Sanofi, Bristol Myers Squibb, Seattle Genetics, CytomX Therapeutics, Daiichi Sankyo, Gilead, Ellipses Pharma, 4D Pharma, OncoSec Medical Inc., BeyondSpring Pharmaceuticals, OncXerna, Zymeworks, Zentalis, Blueprint Medicines, Reveal Genomics, ARC Therapeutics, Infinity Therapeutics, Myovant, Zetagen, Umoja Biopharma, Menarini/Stemline, Aadi Bioscience, Bayer
- **Prof. Frédérique Penault-Ilorca** has received financial support from AbbVie, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Genomic Health, Gilead, GSK, Lilly, Menarini /Stemline, MERCK, MSD, Myriad, NanoString Technologies, Novartis, Pfizer, Pierre-Fabre, Roche, Seagen, Servier, Tesaro; Institutional research grants from AbbVie, Agendia, AstraZeneca, Bayer, BMS, Genomic Health, MSD, Myriad, NanoString Technologies, Roche; Congress invitations from AbbVie, AstraZeneca, BMS, MSD, Novartis, Pfizer, Roche

TODAY YOU WILL

EXPLORE oral SERDs efficacy and safety profiles in patients with ER+/HER2- advanced or metastatic breast cancer and their place in treatment landscape

UNDERSTAND how to optimise treatment selection and sequencing in ER+/HER2- advanced or metastatic breast cancer

KNOW why, when and how to test for *ESR1* mutation in patients with ER+/HER2- advanced or metastatic breast cancer

ER, estrogen receptor; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; SERD, selective estrogen receptor degrader

AGENDA

NEW ORAL ENDOCRINE THERAPY OPTIONS IN BREAST CANCER

Topic	Facilitator	Duration
Welcome & Introductions	COR2ED & Dr Sara Tolaney	5 mins
Overview of Clinical Data of SERDs & Their Place in Treatment Landscape	Dr Aditya Bardia	15 mins
Q&A	All	5 mins
Optimisation of Treatment Selection & Sequencing Decisions in ER+/HER2- Advanced or Metastatic Breast Cancer	Dr Sara Tolaney	15 mins
Q&A	All	5 mins
ESR1 Mutation: The Need for & Role of Testing in ER+/HER2- Advanced or Metastatic Breast Cancer	Prof. Frederique Penault-Llorca	15 mins
Q&A	All	5 mins
Discussion and Questions	All	20 mins
Future Perspectives and Summary	Dr Aditya Bardia	5 mins

ER, estrogen receptor; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; Q&A, questions & answers; SERD, selective estrogen receptor degrader

INTRODUCING THE SCIENTIFIC COMMITTEE

Dr Aditya Bardia

Director of Breast Cancer Research, Associate Professor at Harvard Medical School, Attending Physician at Mass General Cancer Center, USA

Dr Sara Tolaney

Chief, Division of Breast Oncology Dana Farber Cancer Institute, Associate Professor at Harvard Medical School, USA

Prof. Frédérique Penault-Llorca

Professor of Pathology at University of Clermont-Ferrand, CEO of the Comprehensive Regional Cancer Institute Centre Jean PERRIN, Head of the Molecular Biology Platform, Centre Jean Perrin, France

KEY CLINICAL TAKEAWAYS

- **Elacestrant** is the **1st oral SERD to be FDA approved** (January 2023) for postmenopausal women or adult men with ER+/HER2-, ***ESR1*-mutated** advanced or metastatic breast cancer
  - FDA approved Guardant360 CDx assay as a companion diagnostic device to identify patients with ER+/HER2- advanced or metastatic breast cancer for treatment with elacestrant
- With the aim of redefining **treatment landscapes**, for ER+/HER2- advanced and metastatic breast cancer, several **oral SERDs are in clinical development** both as monotherapy and in combination therapy with other targeted therapies, including CDK4/6i
- ***ESR1*, PI3K, CDK4/6, BRCA, and AKT pathways alterations** can be used as targets to guide **treatment selection** and **sequencing decisions** in ER+/HER2- advanced or metastatic breast cancer
- ***ESR1* mutational status** can be determined without repeated tissue biopsy of a metastatic site, instead it can be done reliably by **liquid biopsy at recurrence or progression on ET**

AKT, alpha serine/threonine kinase; BRCA, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CDx, companion diagnostics; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; PI3K, phosphoinositide 3-kinase; SERD, selective estrogen receptor degrader

OVERVIEW OF CLINICAL DATA OF SERDS & THEIR PLACE IN TREATMENT LANDSCAPE

Dr Aditya Bardia

SERD, selective estrogen receptor degrader

POLLING QUESTION

PATIENT CASE OVERVIEW

- 55-year-old female with
  - 2005: HR+/HER2- breast cancer (localised)
  - 2010: Completed adjuvant tamoxifen
  - 2015: Disease recurrence (bone): started letrozole with CDK4/6i
  - 2017: Disease progression (bone)

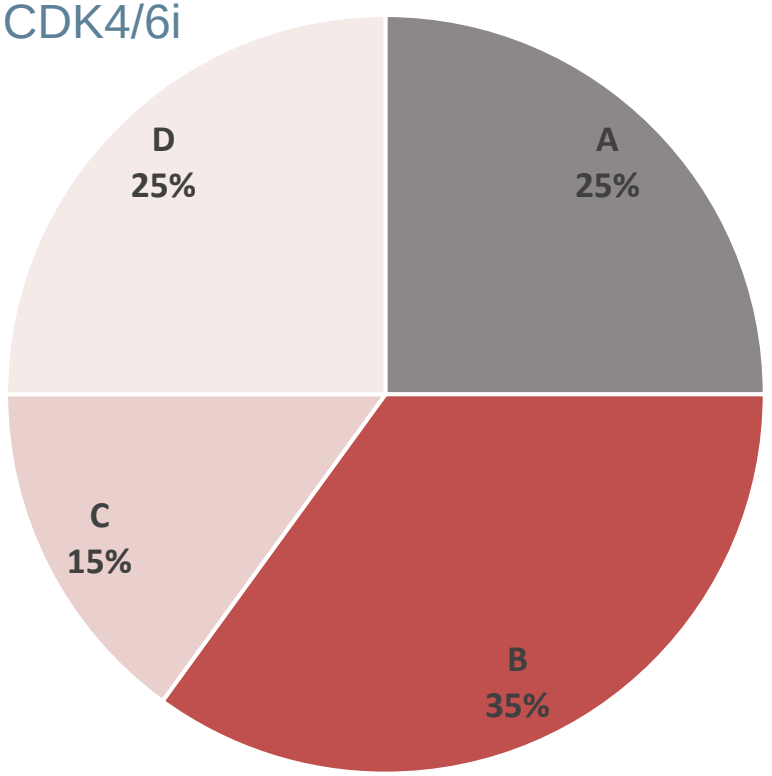
WHICH THERAPY WOULD YOU HAVE CONSIDERED NEXT?

A. Fulvestrant

B. Fulvestrant + CDK4/6i

C. Exemestane + everolimus

D. Clinical trial



CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor

POLLING QUESTION

PATIENT CASE OVERVIEW

- 55-year-old female with
  - 2005: HR+/HER2- breast cancer (localised)
  - 2010: Completed adjuvant tamoxifen
  - 2021: Disease recurrence (bone): started letrozole with CDK4/6i
  - 2023: Disease progression (bone)
  - **ctDNA revealed *ESR1* mutation**

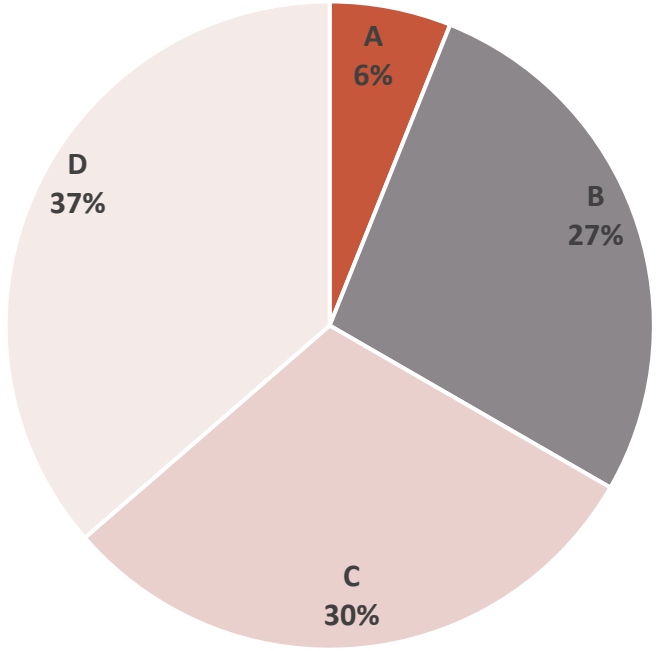
WHICH THERAPY WOULD YOU CONSIDER NEXT?

A. Fulvestrant

B. Fulvestrant + CDK4/6i

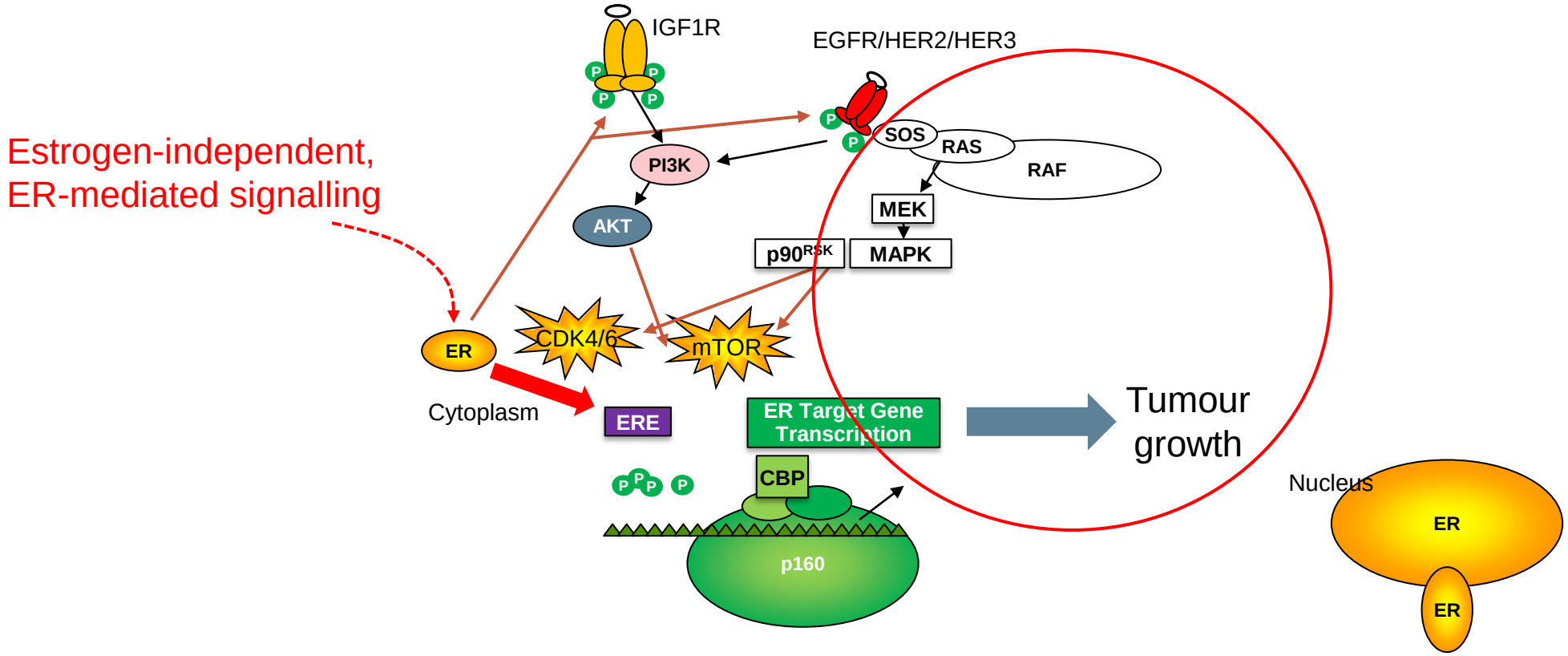
C. Exemestane + everolimus

D. Elacestrant ☑



CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumour DNA; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; HR, hormone receptor

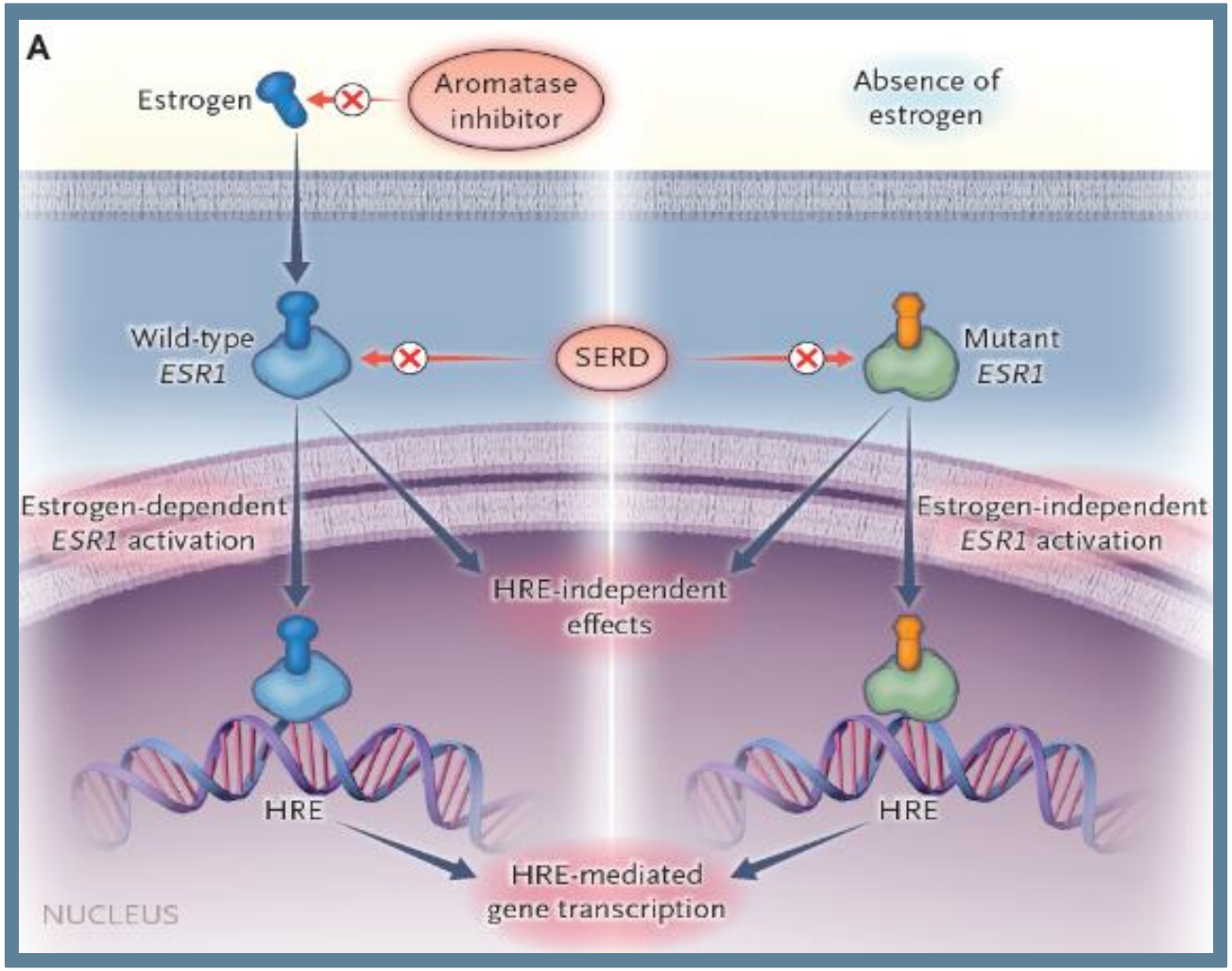
ENDOCRINE THERAPY RESISTANCE: FACTORS TO CONSIDER



AKT, alpha serine/threonine kinase; CBP, CREB binding protein; CDK4/6, cyclin-dependent kinase 4/6; EGFR, epidermal growth factor receptor; ER, estrogen receptor; ERE, estrogen response element; HER2/3, human epidermal growth factor receptor 2/3; IGF1R, insulin-like growth factor 1 receptor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; P, phosphorylation; P90 RSK, ribosomal S6 kinase; PI3K, phosphatidylinositol-3 kinase; SOS, mammalian son-of-sevenless

Johnston SR, J Natl Cancer Inst. 2015;107:djv212

ESR1 (ACQUIRED) MUTATIONS: RESISTANCE TO AI



AI, aromatase inhibitor; ESR1, estrogen receptor 1; HRE, hormone response element; SERD, selective estrogen receptor degrader

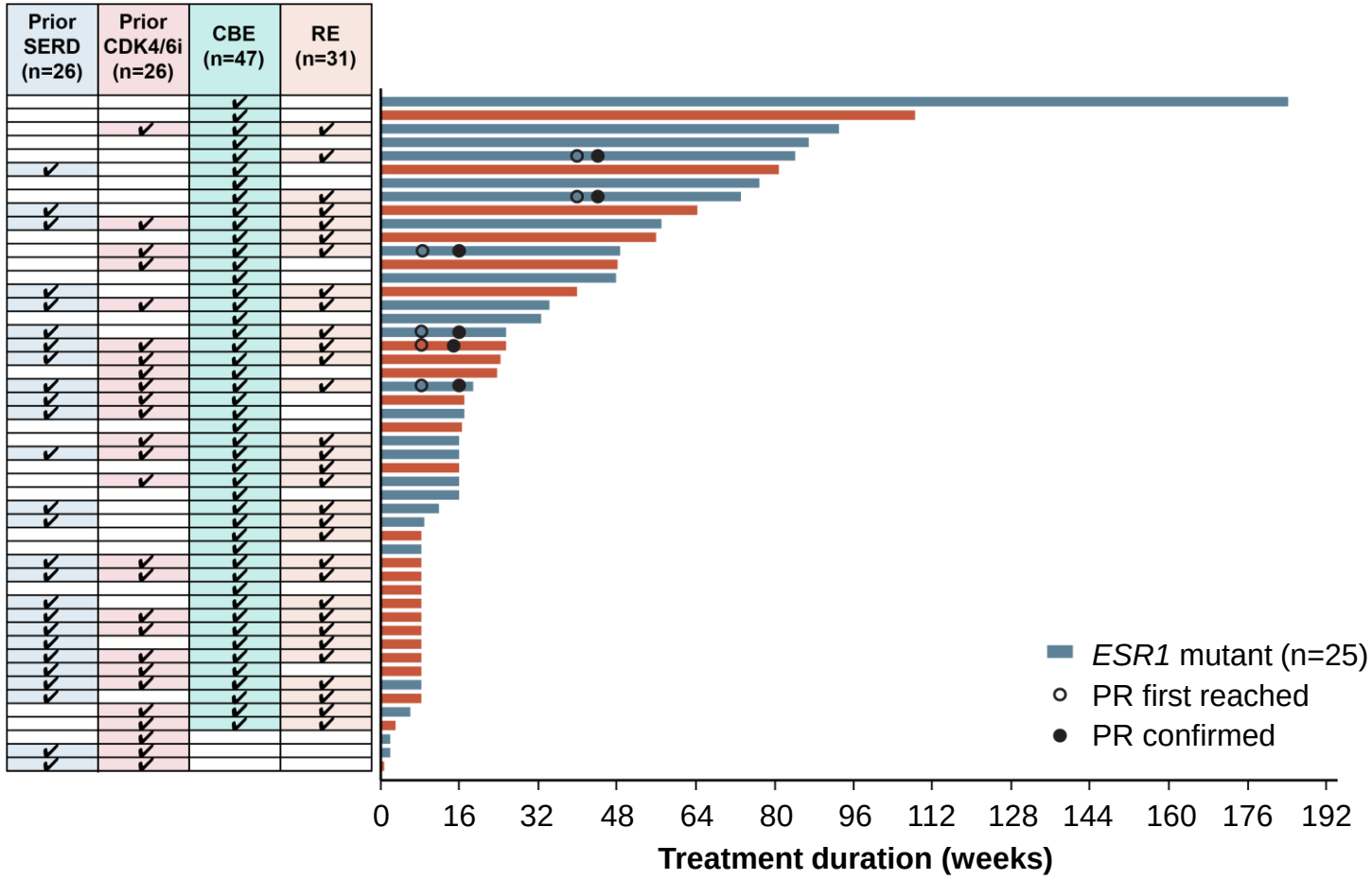
Bardia A, et al. N Engl J Med. 2018;379:1946-53

ELACESTRANT &
THE EMERALD TRIAL

ELACESTRANT CLINICAL ACTIVITY: PHASE 1 TRIAL

CBR AT 24 WEEKS 42.6%

- Median of 3 prior systemic therapies
  - 52% had previously received prior SERD
  - 52% had previously received CDK4/6i therapy
  - 50% had *ESR1* mutation



CBE, clinical benefit–evaluable; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, estrogen receptor 1; PR, partial response; RE, response-evaluable; SERD, selective estrogen receptor degrader

Bardia A, et al. J Clin Oncol. 2021;39:1360-70

PHASE 3 EMERALD: STUDY DESIGN

- A multicentre, international, randomised, open-label, active-controlled phase 3 trial for postmenopausal patients with ER+/HER2- MBC

Key inclusion criteria
Advanced/metastatic ER+/HER2- breast cancer; progressed or relapsed on or after one or two lines of ET, one of which was given in combination with a CDK4/6 inhibitor, for advanced or MBC;
ECOG PS 0 or 1

→ **Elacestrant (400 mg oral QD)**

→ Investigator's choice of fulvestrant, anastrozole, letrozole, exemestane

- **Primary end point:** assess PFS in all patients and those with m*ESR1*
- **Secondary end point:** assess OS in all patients and those with m*ESR1*
- **Study design considerations:**
  - planned sample size: 466 patients (randomised 1:1)
  - planned number of countries/study sites: ~17/215
  - planned study duration: ~30–33 months
  - stratification factors: m*ESR1* status (detected by ctDNA), prior fulvestrant and presence of visceral disease

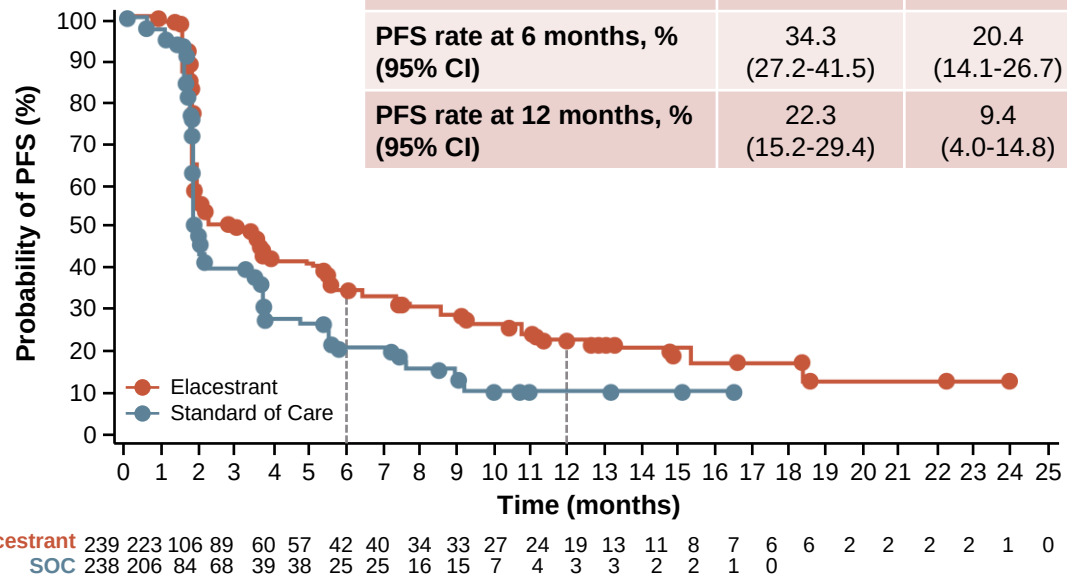
CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumour DNA; DoR, duration of response; ECOG PS; Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2, hormone epidermal growth factor receptor 2; MBC, metastatic breast cancer; mESR1, estrogen receptor 1 mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO patient reported outcome; QD, Use "every day"

Bardia A, et al. SABCS 2021. Abstract GS2-02. Oral presentation

EMERALD: PFS RATE AT 6 & 12 MONTHS ALL PATIENTS AND m*ESR1* GROUP

All patients

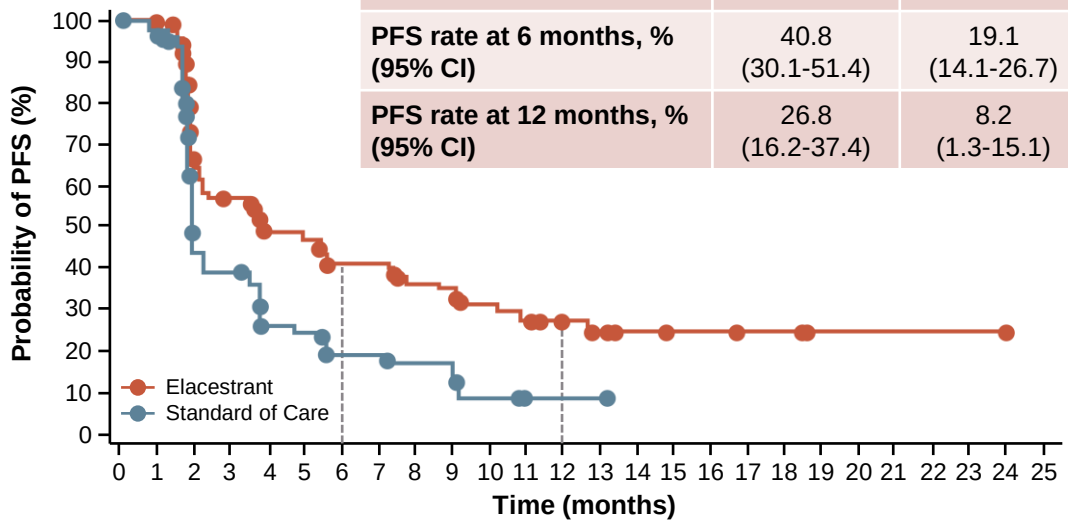
	Elacestrant	SoC
N	**239**	**238**
PFS rate at 6 months, % (95% CI)	34.3 (27.2-41.5)	20.4 (14.1-26.7)
PFS rate at 12 months, % (95% CI)	22.3 (15.2-29.4)	9.4 (4.0-14.8)



Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

Patients with tumours harbouring m*ESR1*

	Elacestrant	SoC
N	**115**	**113**
PFS rate at 6 months, % (95% CI)	40.8 (30.1-51.4)	19.1 (14.1-26.7)
PFS rate at 12 months, % (95% CI)	26.8 (16.2-37.4)	8.2 (1.3-15.1)



Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Elacestrant demonstrated a higher PFS rate versus SoC ET at 6 and 12 months in patients with ER+/HER2- advanced/metastatic breast cancer following prior CDK4/6i therapy

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mESR1, estrogen receptor 1 mutation; N, sample size; PFS, progression-free survival; SoC, standard of care

Bardia A, et al. SABCS 2021. Abstract GS2-02. Oral presentation

POLLING QUESTION

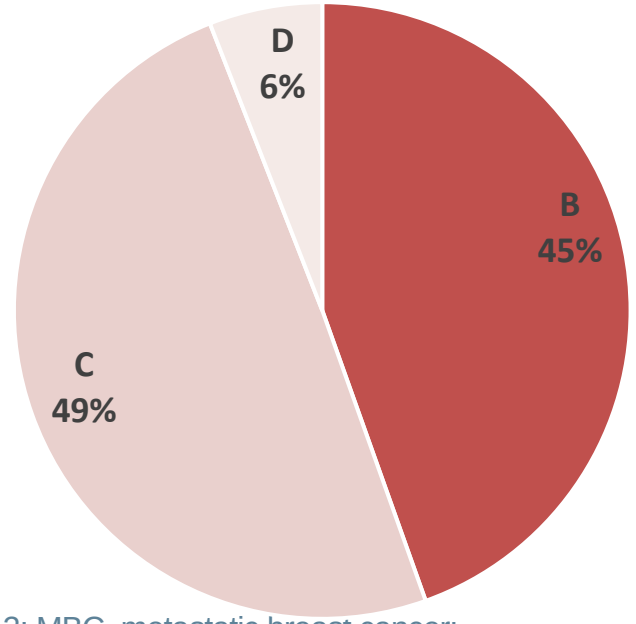
ACCORDING TO DATA PRESENTED IN THE EMERALD TRIAL, WHO OF THE FOLLOWING PATIENTS, WITH ER+/HER2- MBC, WOULD MOST BENEFIT FROM ELACESTRANT TREATMENT?

A. Patients with *ESR1* WT, regardless of prior duration of CDK4/6i

B. Patients with *ESR1* MT and prior duration of CDK4/6i of < 12 months

C. Patients with *ESR1* MT and prior duration of CDK4/6i of >12 months ☑

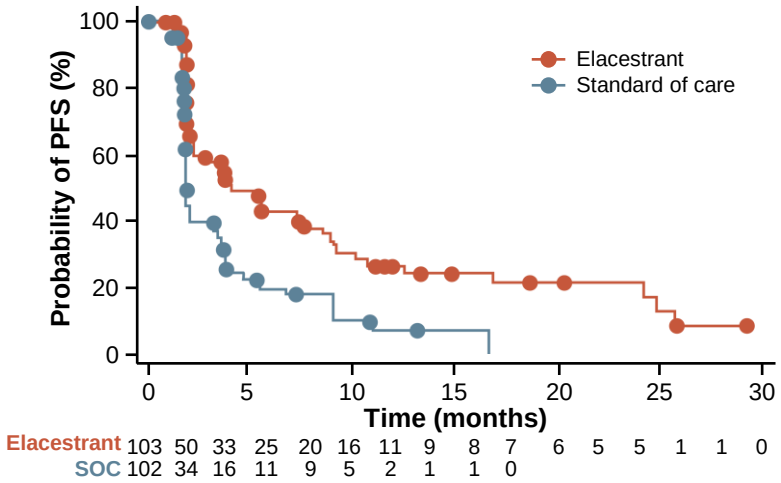
D. All of the above



CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MT, mutation; WT, wild type

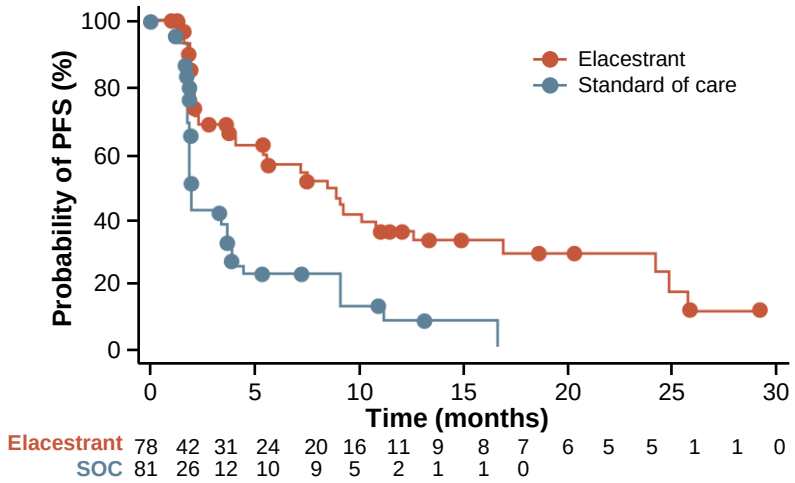
EMERALD: PFS BY DURATION OF CDK4/6i (m*ESR1*)

At least 6 mo CDK4/6i



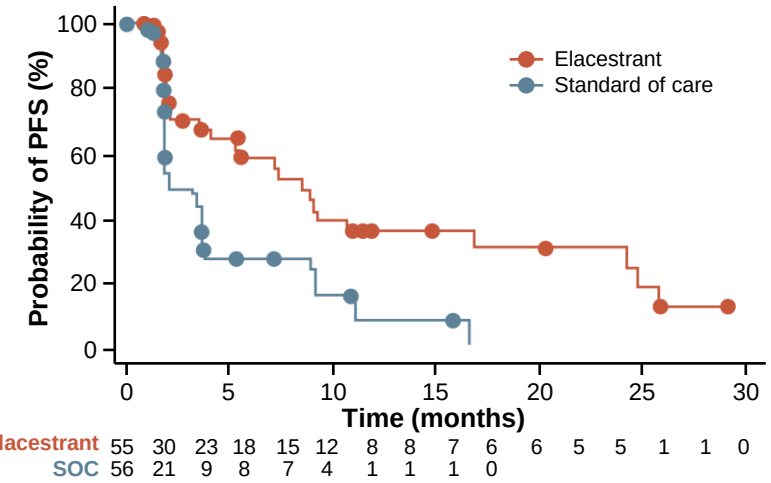
	Elacestrant	SoC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20-7.79)	**1.87** (1.87-3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12-36.92)	6.45 (0.00-13.65)
Hazard ratio (95% CI)	**0.517** (0.361-0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SoC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14-10.84)	**1.91** (1.87-3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84-49.78)	8.39 (0.00-17.66)
Hazard ratio (95% CI)	**0.410** (0.262-0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SoC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45-16.89)	**2.10** (1.87-3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54-52.05)	7.73 (0.00-20.20)
Hazard ratio (95% CI)	**0.466** (0.270-0.791)	

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; mESR1, estrogen receptor 1 mutation; mo, months; PFS, progression-free survival; SoC; standard of care

Bardia A, et al. SABCS 2022. Oral presentation

JANUARY 2023: ELACESTRANT (ORSERDU) APPROVAL

FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

Share | Tweet | Linkedin | Email | Print

On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

ER, estrogen receptor; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer (accessed May 23, 2023)

SAFETY

POLLING QUESTION

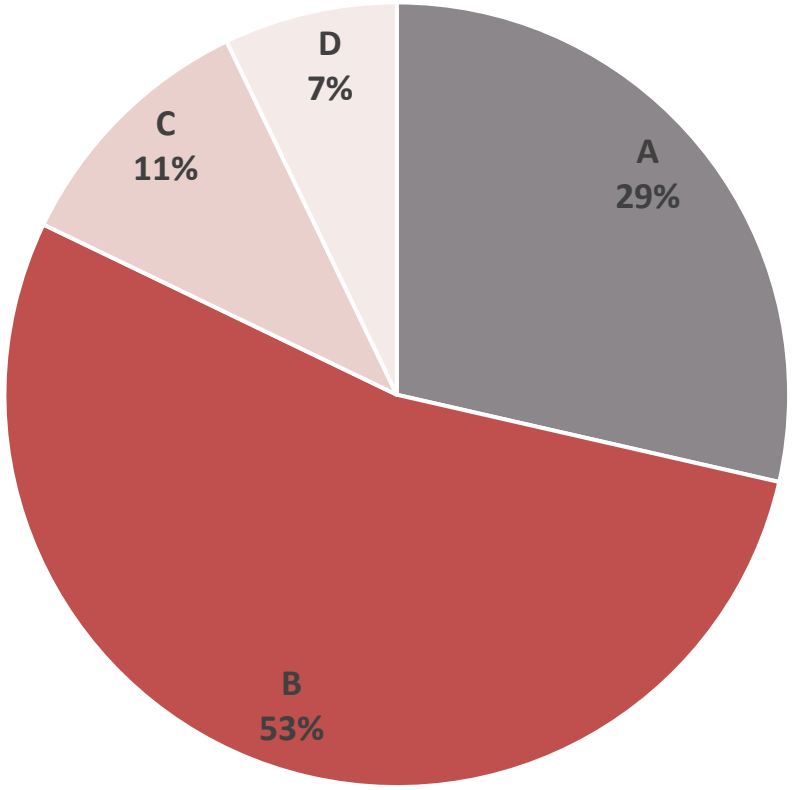
WHAT ARE THE TWO MOST COMMON GRADE 3 OR 4 ADVERSE EVENTS IDENTIFIED WHEN TREATING PATIENTS WITH ELACESTRANT?

A. Diarrhoea and dyspepsia

B. Nausea and arthralgia

C. Nausea and back pain ☑

D. Back pain and fatigue



ELACESTRANT VS SOC: ADVERSE EVENTS

Event	Elacestrant (N=237)	SoC		
		Total (N=229)	Fulvestrant (N=161)	AI (N=68)
Any AE	218 (92.0)	197 (86.0)	144 (89.4)	53 (77.9)
Grade 3 and 4[a]	64 (27.0)	47 (20.5)	33 (20.5)	14 (20.6)
Grade 5[b]	4 (1.7)	6 (2.6)	5 (3.1)	1 (1.5)
Leading to dose reduction	7 (3.0)	0	0	Not applicable
Leading to study drug discontinuation	15 (6.3)	10 (4.4)	6 (3.7)	4 (5.9)

AEs[c] occurring in ≥10% of patients in any arm	Elacestrant		Total		Fulvestrant		AI	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	0	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0	12 (7.5)	0	7 (10.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	0	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0	28 (17.4)	0	9 (13.2)	0
Diarrhoea	33 (13.9)	0	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	0
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	0
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0	18 (11.2)	0	8 (11.8)	0
Constipation	29 (12.2)	0	15 (6.6)	0	10 (6.2)	0	5 (7.4)	0
Hot flush	27 (11.4)	0	19 (8.3)	0	15 (9.3)	0	4 (5.9)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0	4 (2.5)	0	2 (2.9)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	0	6 (8.8)	1 (1.5)

[a]AE severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. [b]No fatal events were attributed to study drug by the investigator. [c]Preferred terms were coded using the Medical Dictionary for Regulatory Activities version 23.0. [d]Grade 1 nausea, n=59 (24.9%); grade 2 nausea, n=18 (7.6%); grade 3 nausea, n= 6 (2.5%); and no patients experienced grade 4 nausea. Percentages reflect maximum grade experienced. [e]Grade 1 vomiting, n=36 (15.2%); grade 2 vomiting, n=7 (3.0%); grade 3 vomiting, n=2 (0.8%); and no patients experienced grade 4 vomiting. Percentages reflect maximum grade experienced

AE, adverse event; AI, aromatase inhibitor; ALT, alanine transaminase; AST, aspartate transferase; n, sample size; SoC, standard of care

https://ascopubs.org/na101/home/literatum/publisher/asco/journals/content/jco/2022/jco.2022.40.issue-28/jco.22.00338/20220921/images/large/jco.22.00338t2.jpeg (accessed May 23, 2023)

OTHER SERDs & TREATMENT LANDSCAPE

SERD, selective estrogen receptor degrader

ORAL SERD IN ER+ MBC: CURRENT DEVELOPMENT STATUS

Drug name	Trial name[a]	Current Development Status
Elacestrant (RAD-1901)	EMERALD[1]	FDA Approved[11]
Giredestrant (GDC-9545)	persevERA[2]	Phase 3
Amcenestrant (SAR439859)	AMEERA-6[3]	Discontinued
Imlunestrant (LY3484356)	EMBER[4]	Phase 3
Camizestrant (AZD9833)	SERENA[5]	Phase 3
Borestrant (ZB716)	ENZENO[6]	Phase 1/2
ZN-c5	NCT03560531[7]	Phase 1/2
Rintodestrant (G1T48)	NCT03455270[8]	Phase 1
D-0502	NCT03471663[9]	Phase 1
LSZ-102	NCT02734615[10]	Phase 1

Need to be careful with cross-study comparisons:

Differences in prior lines of treatment, endocrine sensitivity, tumour biology

ER, estrogen receptor; FDA, Food and Drug Administration; MBC, metastatic breast cancer; SERD, selective estrogen receptor degrader

[1] https://clinicaltrials.gov/ct2/show/NCT03778931?term=ELACESTRANT&phase=2&draw=2&rank=1; [2] https://www.clinicaltrials.gov/ct2/show/NCT04546009;
[3]https://clinicaltrials.gov/ct2/show/NCT05128773?term=Amcenestrant&draw=2&rank=3; [4] https://clinicaltrials.gov/ct2/show/NCT04975308?term=EMBER+phase+3&draw=2&rank=1
[5]https://clinicaltrials.gov/ct2/show/NCT04964934?term=SERENA+phase+3&draw=2&rank=1; [6] https://clinicaltrials.gov/ct2/show/NCT04669587?term=ENZENO&draw=2&rank=1;
[7] https://clinicaltrials.gov/ct2/show/NCT03560531?term=NCT03560531&draw=2&rank=1;[8] https://clinicaltrials.gov/ct2/show/NCT03455270?term=NCT03455270&draw=2&rank=1;
[9] https://clinicaltrials.gov/ct2/show/NCT03471663?term=NCT03471663&draw=1&rank=1; [10] https://clinicaltrials.gov/ct2/show/NCT02734615?term=NCT02734615&draw=2&rank=1
[11]https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer; [a]All references accessed may 22, 2023

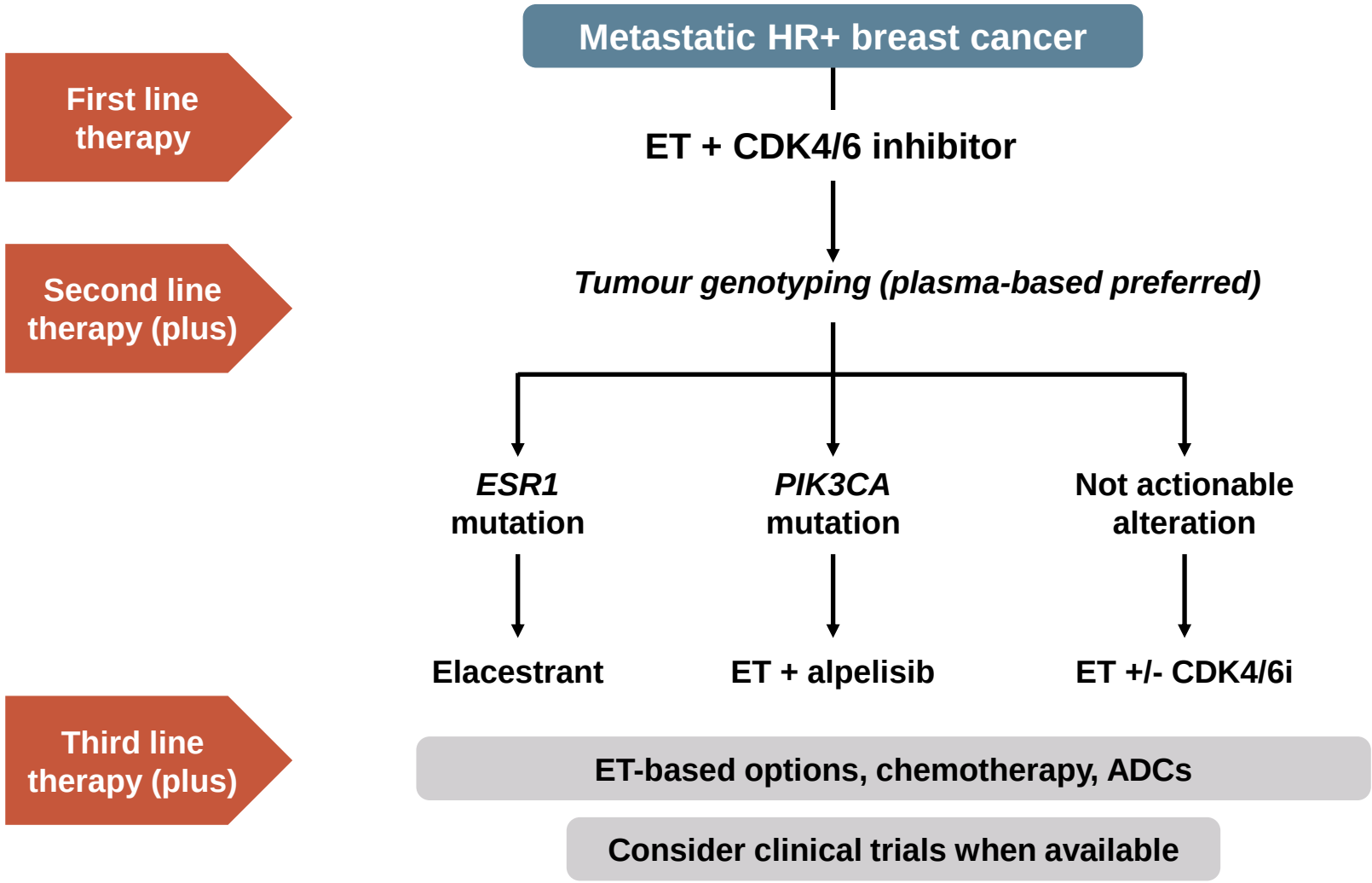
CLOSER LOOK AT ORAL SERDS PHASE 3 TRIALS

	EMERALD[1]	persevERA[2]	SERENA-6[3]	EMBER-3[4]
N	466	992	300	860
PATIENT POPULATION	ER+/HER2- ABC/MBC	ER+/HER2- ABC/MBC	ER+/HER2- MBC with detectable *ESR1* mutation	ER+/HER2- ABC/MBC
PRIOR CHEMO	20% had 1 line[5]	Allowed	Allowed	Not allowed[a]
PRIOR FULV	30%[5]	Not allowed	Not allowed	Not allowed
PRIOR CDK4/6i (advanced/metastatic settings)	Required	Allowed	Required	Allowed
TREATMENT ARMS	Elacestrant vs ET (AI or fulvestrant)	Giredestrant + letrozole-matched placebo + palbociclib vs giredestrant-matched placebo + letrozole + palbociclib	Camizestrant + palbociclib or abemaciclib vs anastrozole or letrozole + palbociclib or abemaciclib	Imlunestrant vs ET (AI or fulv) vs imlunestrant + abemaciclib
PRIMARY ENDPOINT	PFS in ITT[5]	PFS	PFS	PFS
RESULTS	FDA-Approved[6]	Not yet reported Estimated primary completion date: April 2024	Not yet reported Estimated primary completion date: January 2025	Not yet reported Estimated primary completion date: April, 2024

ABC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; chemo, chemotherapy; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; fulv, fulvestrant; HER2, human epidermal growth factor 2; ITT, intent-to-treat; MBC, metastatic breast cancer; N, sample size; PFS, progression-free survival

[1] https://clinicaltrials.gov/ct2/show/NCT03778931?term=ELACESTRANT&phase=2&draw=2&rank=1 (accessed May 22, 2023)
[2] https://www.clinicaltrials.gov/ct2/show/NCT04546009 (accessed May 22, 2023)
[3] https://clinicaltrials.gov/ct2/show/NCT04964934?term=SERENA+phase+3&draw=2&rank=1 (accessed May 22, 2023)
[4] https://clinicaltrials.gov/ct2/show/NCT04975308?term=EMBER+phase+3&draw=2&rank=1 (accessed May 22, 2023) [5]Bidard F-C, et al. J Clin Oncol. 2022;40:3246-56
[61]https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer (accessed May 22, 2023)
[A]Except for neoadjuvant/ adjuvant chemotherapy

HR+ MBC: TREATMENT ALGORITHM



*ADC, antibody drug conjugate; CDK4/6(i), cyclin-dependent kinase 4/6 (inhibitor); ESR1, estrogen receptor 1; ET, endocrine therapy; HR, hormone receptor; MBC, metastatic breast cancer; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Provided by Aditya Bardia

CONCLUSION

OVERVIEW OF CLINICAL DATA OF SERDs & THEIR PLACE IN TREATMENT LANDSCAPE

- Endocrine therapy is the mainstay of management of patient with HR+ MBC
- Elacestrant, an oral SERD, has demonstrated superiority over standard endocrine therapy in second-/third-line setting, and FDA approved for *ESR1* mutant MBC
- Elacestrant exhibited manageable toxicity with most adverse events being of grade 1 or 2 severity
- There are several oral SERDs in clinical development for HR+ metastatic breast cancer, alone and in combination therapy with other targeted therapies, including CDK4/6, PI3K, and AKT inhibitors, which could redefine the therapeutic landscape of breast cancer

AKT, alpha serine/threonine kinase; CDK4/6, cyclin-dependent kinase 4/6; ESR1, estrogen receptor 1; FDA, Food and Drug Administration; HR, hormone receptor; MBC, metastatic breast cancer; PI3K, phosphoinositide 3-kinase; SERD, selective estrogen receptor degrader

DISCUSSION

OPTIMISATION OF TREATMENT SELECTION & SEQUENCING DECISIONS IN ER+ ADVANCED OR METASTATIC BREAST CANCER

Dr Sara Tolaney

ER, estrogen receptor

POLLING QUESTION

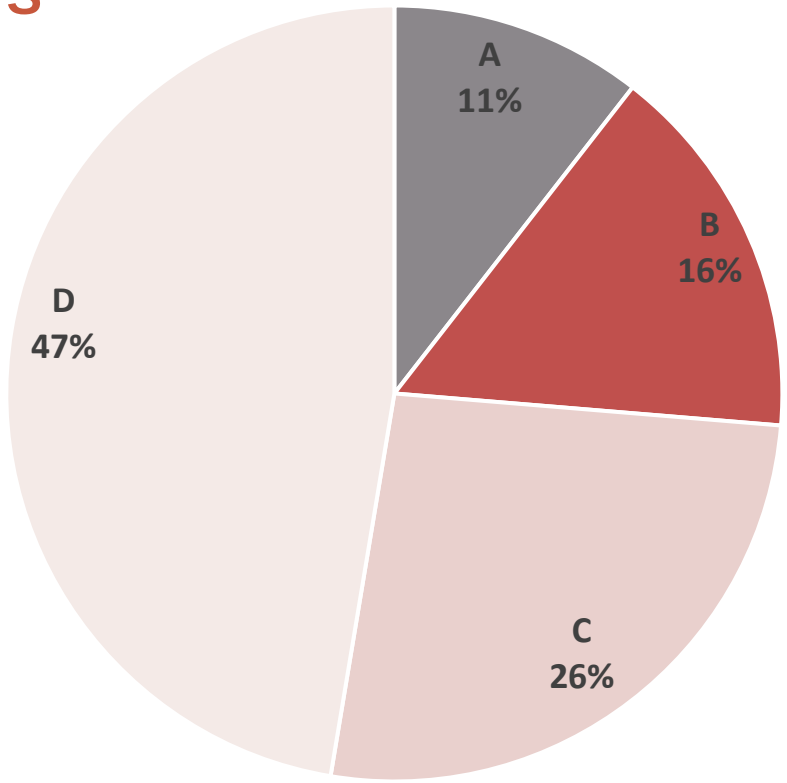
WHAT IS A POTENTIAL SECOND LINE TREATMENT OPTION FOR ER+/HER2- MBC PATIENTS IN CDK4/6i PRETREATED PATIENTS

A. Elacestrant (if m*ESR1*)

B. Fulvestrant + everolimus

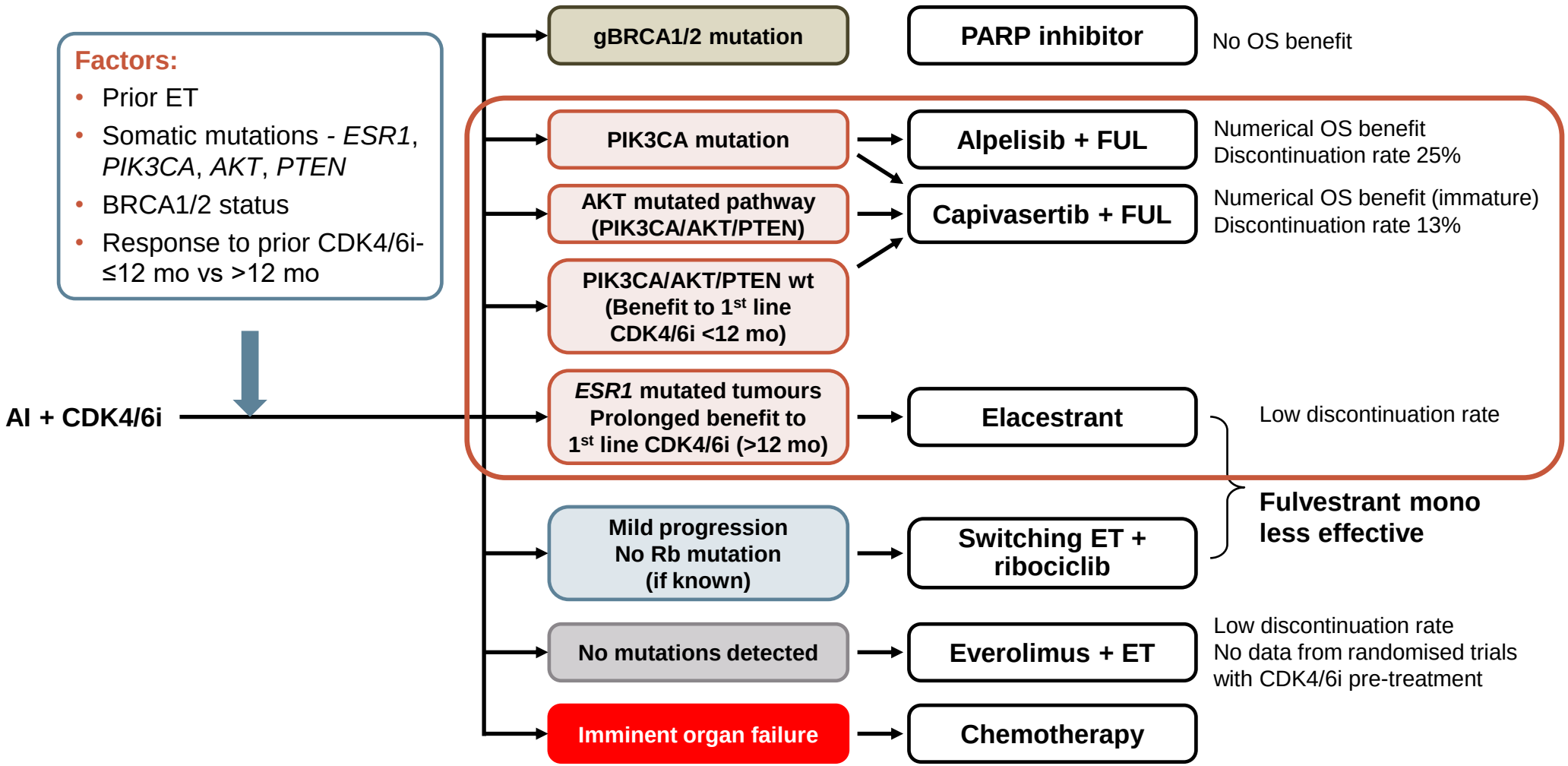
C. Fulvestrant + alpelisib (if mPI3K)

D. All of the above ☑



CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor 2; MBC, metastatic breast cancer; mESR1, estrogen receptor 1 mutation; mPI3K, phosphoinositide 3-kinase mutation

POST CDK4/6i ALGORITHM



AI, aromatase inhibitor; AKT, alpha serine/threonine kinase; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, estrogen receptor 1; ET, endocrine therapy; FUL, fulvestrant; (g)BRCA, (germline) BReast CAncer gene, mo, months; OS, overall survival; PARP, poly ADP ribose polymerase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; Rb, retinoblastoma ; wt, wild type

Provided by Sara Tolaney

PI3K INHIBITION

PI3K, phosphoinositide 3-kinase

POLLING QUESTION

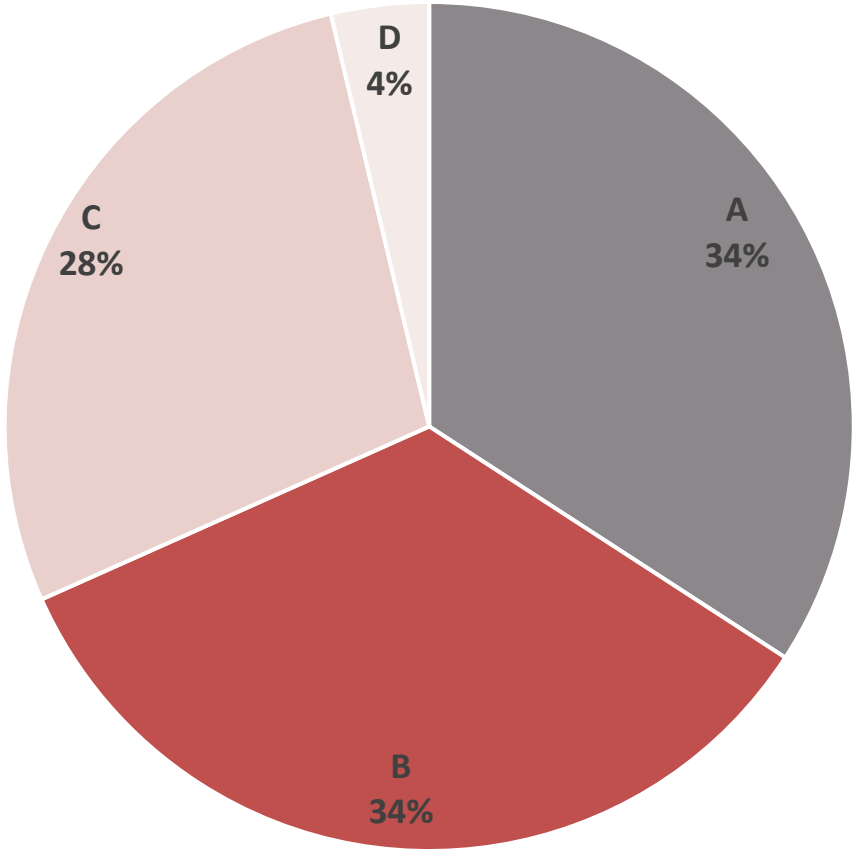
WHAT PERCENTAGE OF HR+ METASTATIC BREAST CANCER HARBOR A PIK3CA MUTATION?

A. ~15%

B. ~25%

C. ~40% ☑

D. ~50%

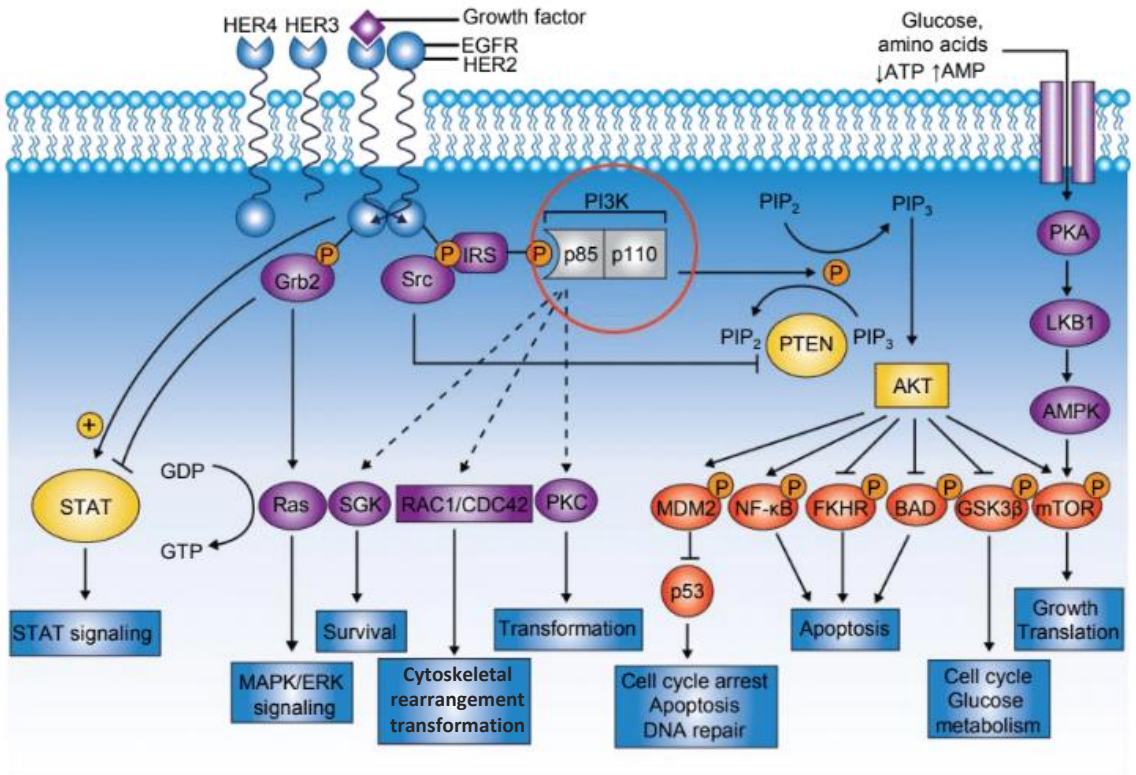


HR, hormone receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

ROLE OF PI3K PATHWAY IN HR+ BC

- PI3K/mTOR pathway is frequently altered in HR+ BC and has been implicated in resistance to endocrine therapies[1,2]
- ≈40% of HR+ BC harbour a *PIK3CA* mutation, leading to hyperactivation of the PI3K pathway[3-5]
- PI3K signalling promotes estrogen-independent growth of ER+ BC cells, and this growth is inhibited by the addition of PI3K inhibitors to antiestrogens[6-8]

PI3K/AKT Pathway[9]



AKT, alpha serine/threonine kinase; AMP, adenosine monophosphate; AMPK, AMP activated protein kinase; ATP, adenosine triphosphate; BAD; Bcl-2-associated death promoter; BC, breast cancer; EGFR, epidermal growth factor receptor; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; FKHR, forkhead transcription factor; GDP, guanosine diphosphate; Grb2, growth factor receptor-bound protein 2; GSK3β, glycogen synthase kinase-3 beta; GTP, nucleotide guanosine triphosphate; HER, human epidermal growth factor, HR, hormone receptor; IRS, insulin receptor substrate; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; MDM2, mouse double minute 2 homolog; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; P, phosphorylation; PI3K,phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PKA/C, protein kinase A/C; PIP, prolactin-induced protein; PTEN, phosphatase and tensin homolog; STAT, signal transducer and activator of transcription

1. Miller TW, et al. J Clin Oncol. 2011;29:4452-61; 2. Bosch A, et al. Sci Transl Med. 2015;7283ra51; 3. Mayer IA, et al. Clin Cancer Res. 2017;23:26-34; 4. Loi S, et al. Proc Natl Acad Sci. 2010;107:10208-13; 5. Stemke-Hale K, et al. Cancer Res. 2008;68:6084-91; 6. Miller TW, et al. J Clin Invest. 2010;120:2406-13; 7. Crowder RJ, et al. Cancer Res. 2009;69:3955-62; 8. Miller TW, et al. Cancer Discov. 2011;1:338-51; 9. Hennessy BT, et al. Nat Rev Drug Discov. 2005;4:988-1004

BYLieve: ALPELISIB + FULVESTRANT IN PIK3CA-MUTANT HR+/HER2- ABC

INTERNATIONAL, OPEN-LABEL, MULTICOHORT, NONCOMPARATIVE PHASE 2 STUDY

- Men and pre-/post-menopausal women with *PIK3CA* mutated HR+/*HER2*- advanced BC
- Immediate prior treatment CDK4/6i and ET, systemic CT, or ET
- No prior PI3Ki
- Measurable disease or ≥1 predominantly lytic bone lesion
- ECOG PS ≤2

Planned N=340

R

Cohort A: Prior CDK4/6i + AI

Alpelisib 300 mg PO QD **+ fulvestrant** 500 mg IM[b,c] (n=119)

Cohort B: Prior CDK4/6i + Fulvestrant

Alpelisib 300 mg PO QD **+ letrozole** 2.5 mg PO QD[c] (minimum n=114)

Cohort C: Prior AI then CT or ET

Alpelisib 300 mg PO QD **+ fulvestrant** 500 mg IM[b,c] (minimum n=115)

- **Primary endpoint:** proportion of each cohort alive without PD at 6 months (RECIST v1.1)
  - Endpoint met if lower 95% CI >30%
- **Secondary endpoints (in each cohort):** PFS, PFS2, ORR, CBR, DoR, OS, and safety

[a]Centrally confirmed. [b]Fulvestrant given on days 1 and 15 of cycle 1, day 1 for subsequent cycles. [c]Men in letrozole cohort and premenopausal women received goserelin 3.6 mg SC Q28D or leuprolide 7.5 mg IM Q28D for adequate gonadal suppression

ABC, advanced metastatic breast cancer; AI, aromatase inhibitor; BC, breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; CT, chemotherapy; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, hormone epidermal growth factor 2; HR, hormone receptor; IM; intramuscular; ORR, objective response rate; OS, overall survival; PD, disease progression; PFS(2), progression-free survival (2); PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PI3Ki, phosphoinositide 3-kinases inhibitor; PO QD, orally once per day; Q28D, every 28 days; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SC, subcutaneous

Chia S. ASCO 2023. Abstract 1078. Oral presentation

ACTIVITY WITH PI3K INHIBITORS & VARIOUS ENDOCRINE PARTNERS

MEDIAN PFS & OS PER LOCAL INVESTIGATOR ASSESSMENT IN 2L & 3L

	Cohort A (ALP + FUL)		Cohort B (ALP + LET)		Cohort C (ALP + FUL)	
	Second-line n=95	Third-line n=22	Second-line n=60	Third-line n=52	Second-line n=40	Third-line n=70
PFS events, n[a] (%)	81 (85.3)	16 (72.7)	52 (86.7)	43 (82.7)	28 (70.0)	59 (84.3)
Median follow-up, mo	6.05	6.78	5.34	4.85	5.59	5.49
Median PFS, mo (95% CI)[b]	8.1 (5.6-9.5)	8.0 (3.6-18.4)	5.6 (3.5-9.1)	5.9 (3.7-7.1)	6.7 (4.8-10.2)	5.5 (5.4-8.3)
OS events, n[a] (%)	56 (58.9)	14 (63.6)	31 (51.7)	34 (65.4)	17 (42.5)	38 (54.3)
Median follow-up, mo	24.08	19.86	28.99	21.62	19.47	18.22
Median OS, mo (95% CI)[b]	27.8 (21.3-37.3)	21.3 (15.4-32.7)	34.1 (25.0-37.4)	24.8 (15.6-30.4)	NE (16.3-NE)	20.7 (16.3-28.1)

2L, second line of treatment; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mo, months; NA, not applicable; PFS progression free survival; PI3K(i), phosphoinositide 3-kinase (inhibitor); PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; tx, treatment

Hope R. et al, SABCS 2021. Oral presentation; Hope R. et al. Cancer Res 2021; 81 (4): PD2-07

AKT INHIBITION

AKT, alpha serine/threonine kinase

CAPIVASERTIB + FULVESTRANT IN AI- RESISTANT HR+/HER2- BC

CAPItello-291 PHASE 3 STUDY DESIGN

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumour sample from the primary/recurrent cancer available for retrospective central molecular testing

R
1:1
(N=708)

Capivasertib: 400 mg twice daily, 4 days on, 3 days off

Fulvestrant: 500 mg: cycle 1, days 1 and 15; then every 4 weeks

Stratification factors:

- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region

Placebo: twice daily, 4 days on, 3 days off

Fulvestrant: 500 mg: cycle 1, days 1 and 15; then every 4 weeks

Dual primary endpoints

PFS by investigator assessment

- Overall
- AKT pathway-altered tumours (≥1 qualifying *PIK3CA, AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival

- Overall
- AKT pathway-altered tumours

Objective response rate

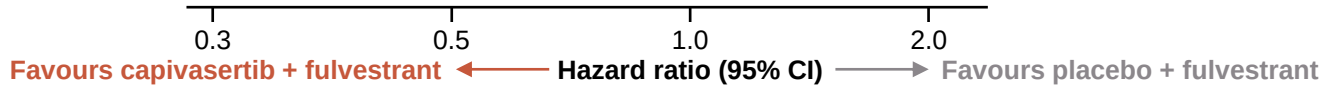
- Overall
- AKT pathway-altered tumours

ABC, advanced breast cancer; AI, aromatase inhibitor; AKT, alpha serine/threonine kinase; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; FFPE, formalin-fixed paraffin-embedded; HbA1c, haemoglobin A1c; HER2, human epidermal growth factor receptor; HR, hormone receptor; mTOR, mammalian target of rapamycin; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; R, randomisation; SERD, selective estrogen receptor degrader

Presented by Nick Turner, SABCS 2022. Oral presentation

INVESTIGATOR ASSESSED PFS BY SUBGROUP

		Number of patients	HR (95% CI)
All patients		**708**	**0.60 (0.51, 0.71)**
Age	<65 years	491	0.65 (0.53, 0.79)
	≥65 years	217	0.65 (0.47, 0.90)
Race	Asian	189	0.62 (0.44, 0.86)
	White	407	0.65 (0.52, 0.80)
	Other	112	0.63 (0.42, 0.96)
Region	1	395	0.60 (0.48, 0.75)
	2	136	0.77 (0.51, 1.16)
	3	177	0.60 (0.42, 0.85)
Menopausal status (females only)	Pre/peri	154	0.86 (0.60, 1.20)
	Post	547	0.59 (0.48, 0.71)
Liver metastases	Yes	306	0.61 (0.48, 0.78)
	No	402	0.62 (0.49, 0.79)
Visceral metastases	Yes	478	0.69 (0.56, 0.84)
	No	230	0.54 (0.39, 0.74)
Endocrine resistance	Primary	262	0.66 (0.50, 0.86)
	Secondary	446	0.64 (0.51, 0.79)
Prior use of CDK4/6 inhibitors	Yes	496	0.62 (0.51, 0.75)
	No	212	0.65 (0.47, 0.91)
Prior chemotherapy for ABC	Yes	129	0.61 (0.41, 0.91)
	No	579	0.65 (0.54, 0.78)



ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Presented by Nick Turner, SABCS 2022. Oral presentation

CDK4/6 INHIBITION

CDK4/6, cyclin-dependent kinase 4/6

POLLING QUESTION

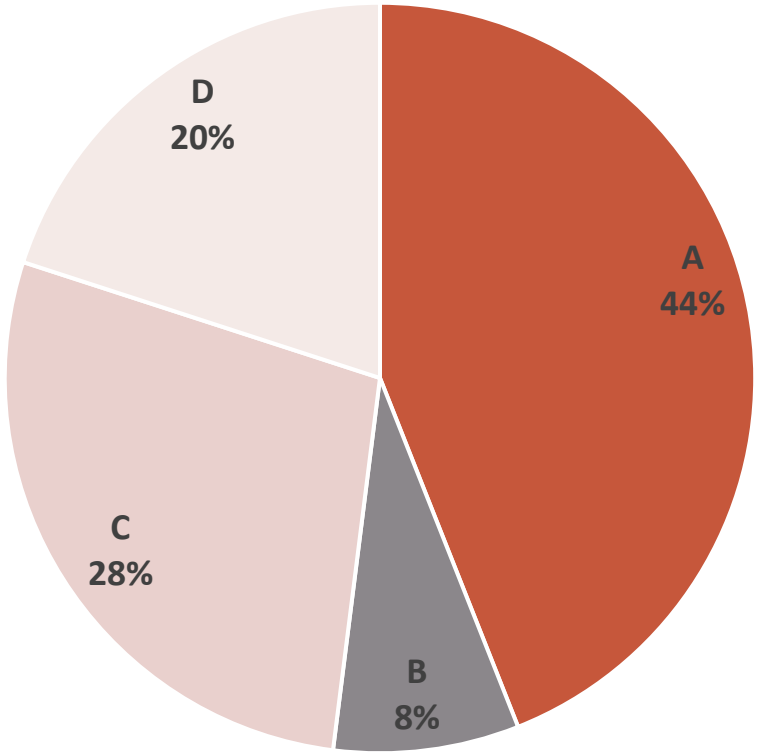
IS THERE A ROLE FOR CONTINUATION OF CDK4/6 INHIBITION BEYOND PROGRESSION?

A. YES

B. NO

C. MAYBE

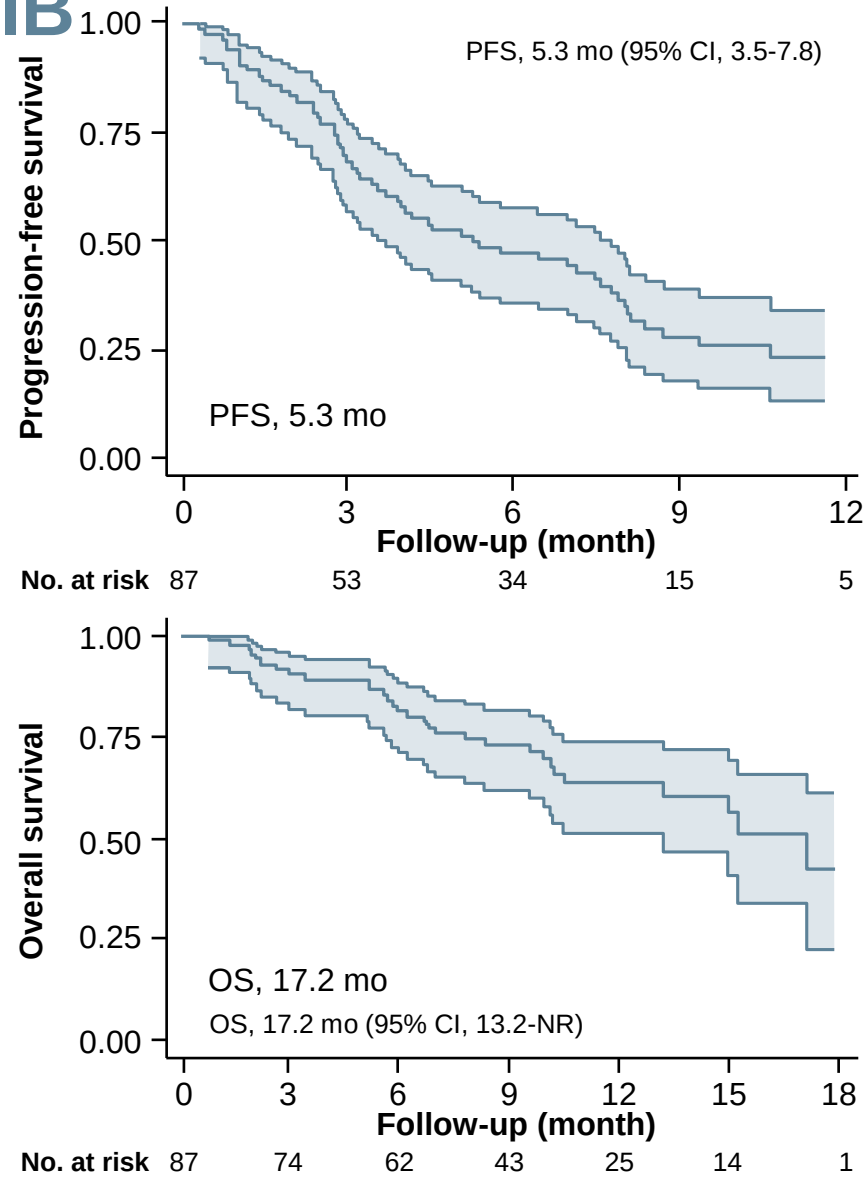
D. I DON'T KNOW



CDK4/6, cyclin-dependent kinase 4/6

CASE SERIES: ABEMA POST PALBOCICLIB

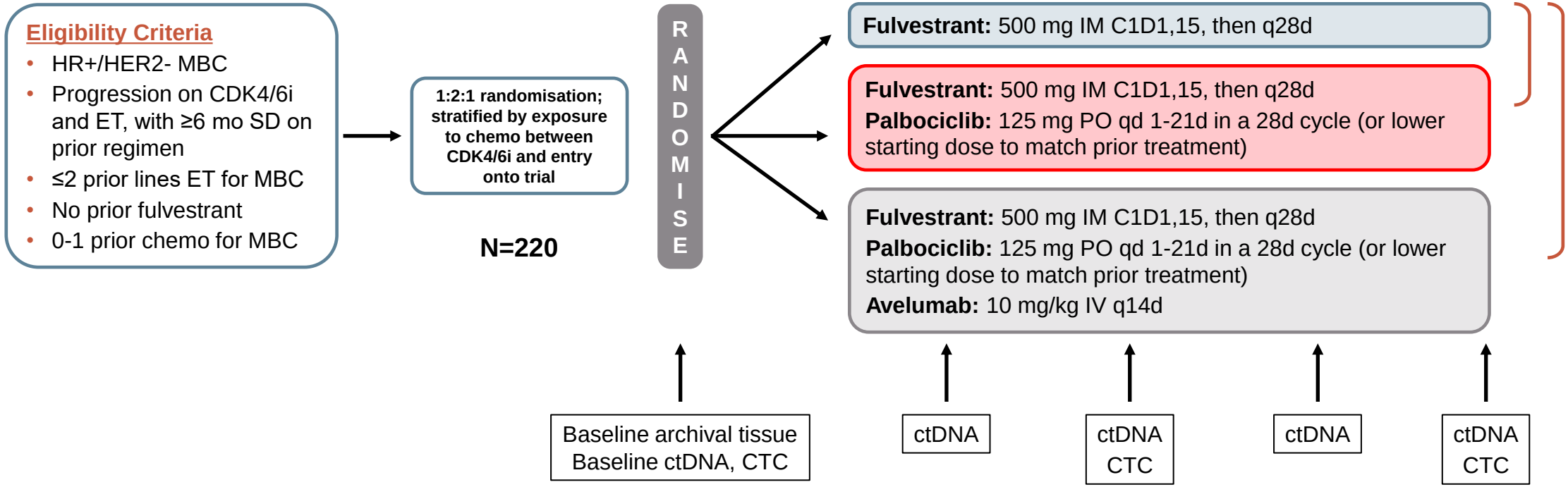
- Six-institution retrospective analysis
  - 87 pts treated with abemaciclib post palbociclib/ribociclib
  - 9.2% stopped abema due to toxicity without progression
  - 71.3% received non-sequential therapy with >1 intervening non-CDK4/6i regimen
  - Endocrine partners: FULV: 47.1%; AI: 27.6%; monotherapy, 19.5%
- Efficacy
  - Subset of patients derived clinical benefit (with 36.8% received abema for ≥ 6 mo)
  - No relationship between the duration of clinical benefit on palbo and subsequent duration of treatment on abema
- Rapid progression on abema associated with RB1, ERBB2, and CCNE1 alterations were noted among patients with rapid progression on abema



abema, abemaciclib; AI, aromatase inhibitor; CCNE1, cyclin E1; CDK4/6(i), cyclin-dependent kinase 4/6 (inhibitor); CI, confidence interval; pts, patients; ERBB2, v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2; FULV, fulvestrant; mo, months; NR, not reached; OS, overall survival; PFS, progression-free survival; RB1, retinoblastoma protein

Wander SA, et al. J Natl Compr Canc Network. 2021; doi: 10.6004/jnccn.2020.7662. Online ahead of print

PACE TRIAL : PALBOCICLIB AFTER CDK & ET IN HR+ MBC



Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs fulvestrant alone

Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, safety, outcomes in predefined molecular subgroups including *ESR1*, *PIK3CA*, and *Rb*

C1D1, cycle 1 day 1; CDK4/6i, cyclin-dependent 4/6 inhibitor; chemo, chemotherapy; CTC, circulating tumour cell; ctDNA, circulating tumour DNA; d, day; ESR1, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IM, intramuscular; IV, intravenous; MBC, metastatic breast cancer; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO, orally; qd, every day; Rb, retinoblastoma; RECIST, response evaluation criteria in solid tumours; SD, stable disease

Presented by Erica Mayer, ASCO 2022. Oral presentation

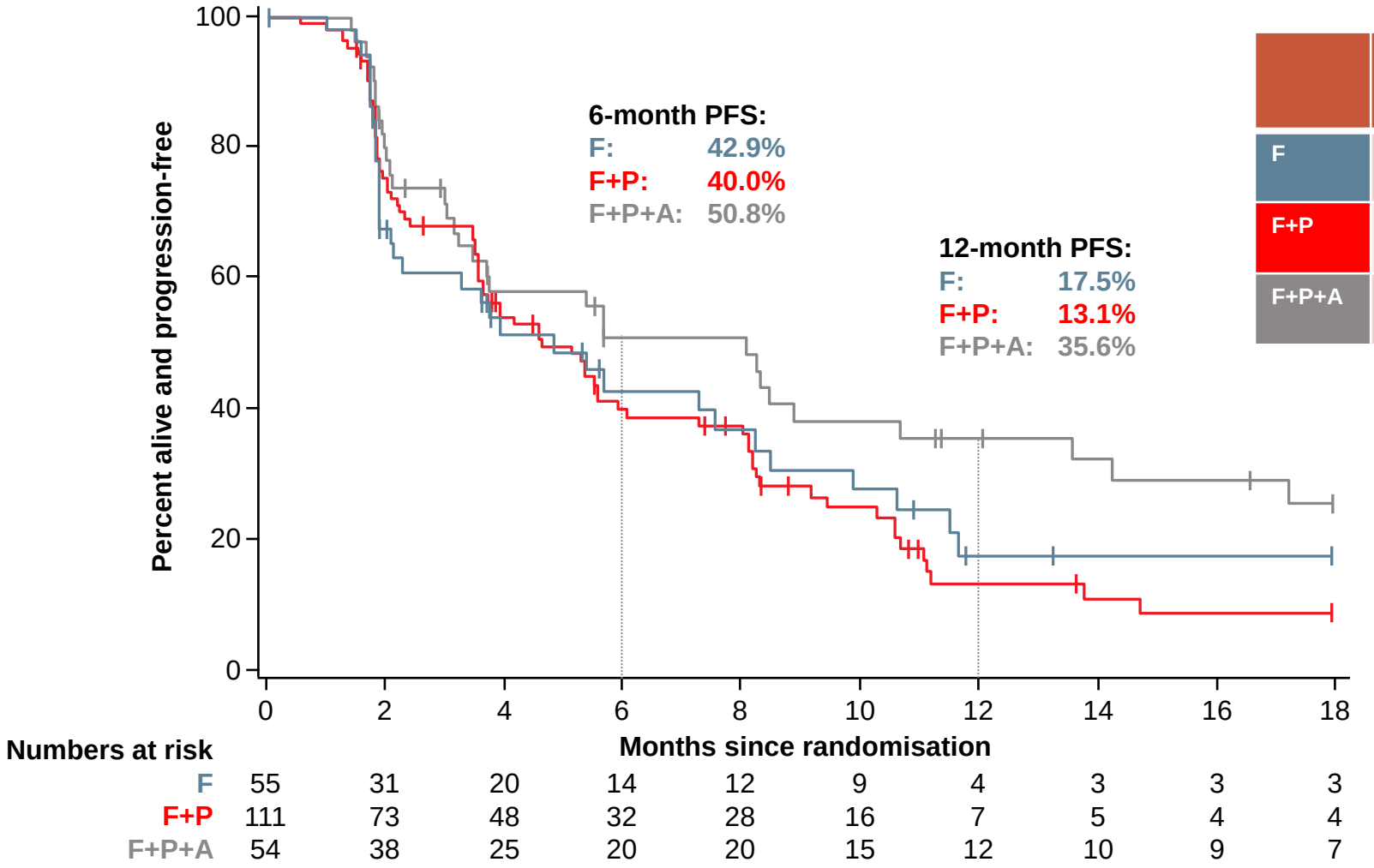
PACE TRIAL: PRIOR TREATMENT CHARACTERISTICS

	Fulvestrant (n=55)		Fulvestrant + palbociclib (N=111)		Fulvestrant + palbociclib + avelumab (N=54)		Overall (N=220)	
	N	%	N	%	N	%	N	%
Prior adjuvant endocrine exposure								
Endocrine resistant	10	**18.2**	32	**28.8**	16	**29.6**	58	**26.4**
Endocrine sensitive	45	**81.8**	78	**70.3**	37	**68.5**	160	**72.7**
Prior CDK4/6i								
Palbociclib	52	**94.5**	102	**19.9**	46	**85.2**	200	**90.9**
Ribociclib	1	**1.8**	5	**4.5**	4	**7.4**	10	**4.5**
Abemaciclib	2	**3.6**	3	**2.7**	4	**7.4**	9	**4.1**
Duration of prior CDK4/6i + ET								
6-12 months	10	**18.2**	26	**23.4**	16	**29.6**	52	**23.6**
>12 months	45	**81.8**	84	**75.7**	38	**70.4**	167	**75.9**
Prior chemotherapy for MBC	11	**20.0**	16	**14.4**	9	**16.7**	36	**16.4**
Line of MBC therapy initiated in PACE								
First line	3	**5.5**	5	**4.5**	2	**3.7**	10	**4.5**
Second line	42	**76.4**	83	**74.8**	44	**81.5**	169	**76.8**
> Second line	10	**18.2**	21	**18.9**	7	**13.0**	38	**17.3**
Any systemic therapy between prior CDK4/6i and randomisation	5	**9.1**	16	**14.4**	5	**9.3**	26	**11.8**

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; MBC, metastatic breast cancer; N, sample size

Presented by Erica Mayer, ASCO 2022. Oral presentation

PACE TRIAL: PROGRESSION FREE SURVIVAL ITT

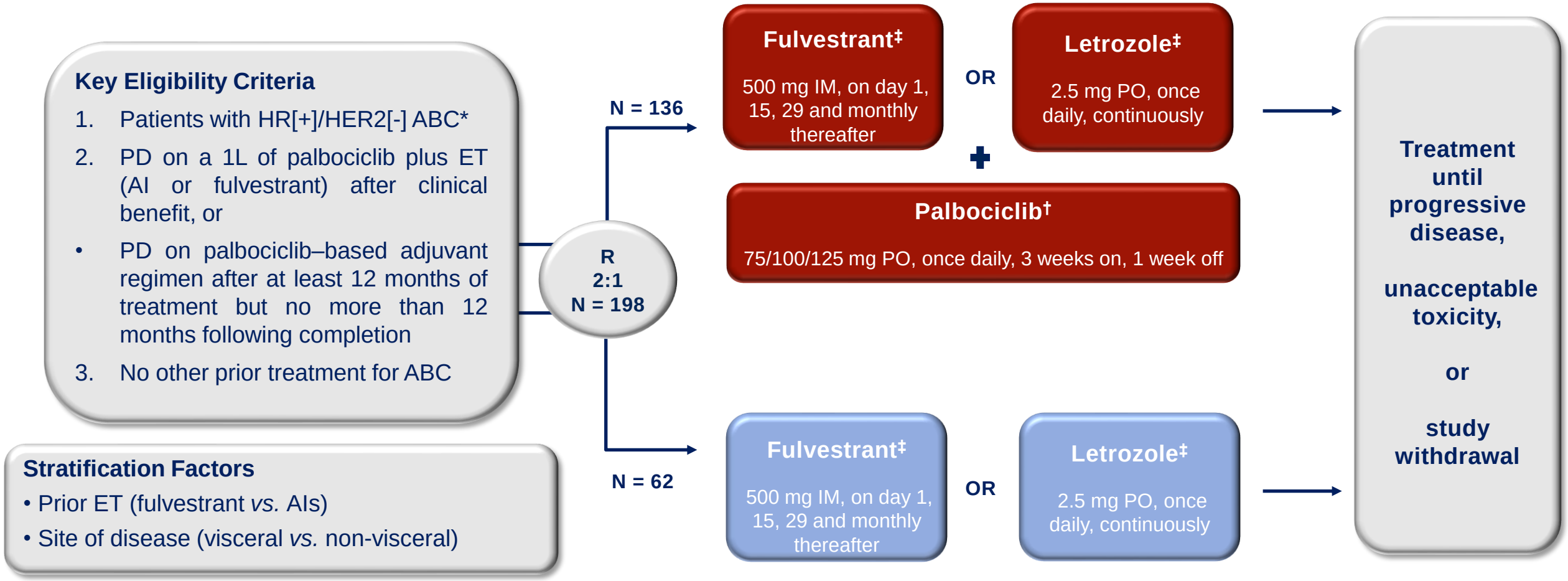


	Pts	PFS events	Median PFS, mo (90% CI)	HR vs F (90% CI)	p value
F	55	34	**4.8** (2.1, 8.2)	–	–
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	0.23

A, avelumab; CI, confidence interval; F, fulvestrant; HR, hazard ratio; ITT, intention to treat; mo, months; P, palbociclib; PFS, progression free survival; pt, patient

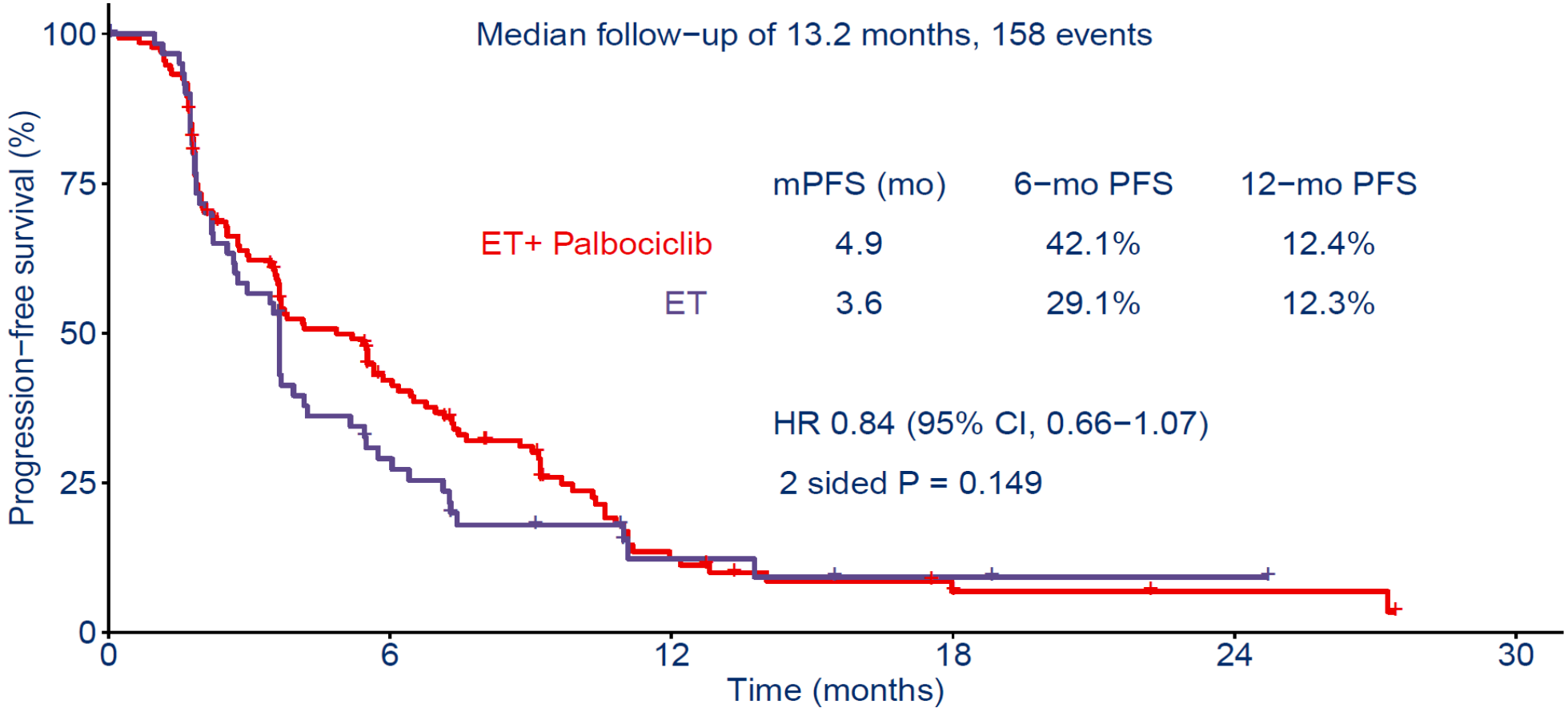
Presented by Erica Mayer, ASCO 2022. Oral presentation

PALMIRA Study Design (NCT03809988)



1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.
*If pre-menopausal, ovarian function suppression method required.
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.
‡Administration of endocrine therapy was chosen depending on the prior administered agent.

Primary Objective: Investigator-assessed PFS (ITT Population)



Patients at risk, n (%)

ET+Palbociclib	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

Llombard Cussac A et al, ASCO 2023

ONGOING CDK4/6 SEQUENCING TRIALS IN HR+ BC

KEY TRIALS IN PROGRESS

Trial	Patient Population	Treatment Arms	N (est), (R)	Endpoints	Est. PCD
postMONARCH[1] (Phase 3)	• HR+/HER2- mBC • Disease progression on 1L CDK4/6i + AI **OR** disease recurrence on or after CDK4/6i + ET in the adjuvant setting	• **Arm 1**: ABM + FUL • **Arm 2**: PBO + FUL	350 (1:1)	• **Primary**: PFS (by investigator assessment, RECIST v1.1) • **Secondary:** OS, ORR, CBR, DoR, PROs, safety, pharmacokinetics	August 2023
EIAINE-3[2] (Phase 3)	• ER+/HER2- locally advanced or mBC with m*ESR1* • Progressed on an AI in combination with either PALBO or RIBO in 1L	• **Arm 1**: LASO + ABEMA • **Arm 2**: FUL + ABEMA	400 (2:1)	• **Primary**: PFS, according to RECIST v1.1 • **Secondary:** OS, ORR, CBR, DoR, QoL, TCC, TRR, safety	June 2025
EMBER-3[3] (Phase 3)	• ER+/HER2- locally advanced or mBC • Disease progression on or after treatment with AI ± CDK4/6i	• **Arm 1**: Imlunestrant • **Arm 2**: Imlunestrant + ABM • **Arm 3:** investigator's choice of ET	860	• **Primary**: PFS in ITT population and in the *mESR1* population • **Secondary:** OS (in the ITT population and in the *mESR1* population), ORR, DoR, CBR, PFS, PROs	April 2024

1L, first line; aBC, advanced breast cancer; ABM, abemaciclib; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin dependent kinase 4/6 inhibitor; DoR, duration of response; ER, estrogen receptor; est, estimated; ET, endocrine therapy; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intention to treat; LASO, lasofoxifene; mBC, metastatic breast cancer; mESR1, estrogen receptor 1 mutation; N, sample size; PAL, palbociclib; PFS, progression-free survival; PRO patient reported outcome; ORR, objective response rate; OS, overall survival; PCD, primary completion date; QoL, quality of life; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; TCC, time to cytotoxic chemotherapy; TTC, time to chemotherapy; TTR, time to response

1. Kalinsky K, et al. ASCO 2022. Poster TPS1117; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05696626?term=ELAINEIII&cond=BReast+cancer&draw=2&rank=1 (accessed May 22, 2023);
3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04975308 (accessed May 22, 2023)

CONCLUSION

SHOULD WE BE SWITCHING ET AND CDK4/6I ROUTINELY IN THE SECOND LINE SETTING?

- Maybe a reasonable strategy for select patients with use of ribociclib or abemaciclib (i.e. lack of Rb mutation)
- No role for palbociclib beyond progression at this time
- Unclear if need to switch both ET and CDK4/6i
- Will need to better understand genomic predictors of benefit/resistance
- Will need to await data from other continuation trials for a better understanding

CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ET, endocrine therapy; Rb, retinoblastoma

DISCUSSION

ESR1 MUTATION: THE NEED FOR & ROLE OF TESTING IN ER+/HER2- METASTATIC BREAST CANCER

Prof. Frédérique Penault-Llorca

ER, estrogen receptor; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2

USEFUL BIOMARKERS: METASTATIC OR LOCALLY ADVANCED UNRESECTABLE BREAST CANCER HR+/HER2-

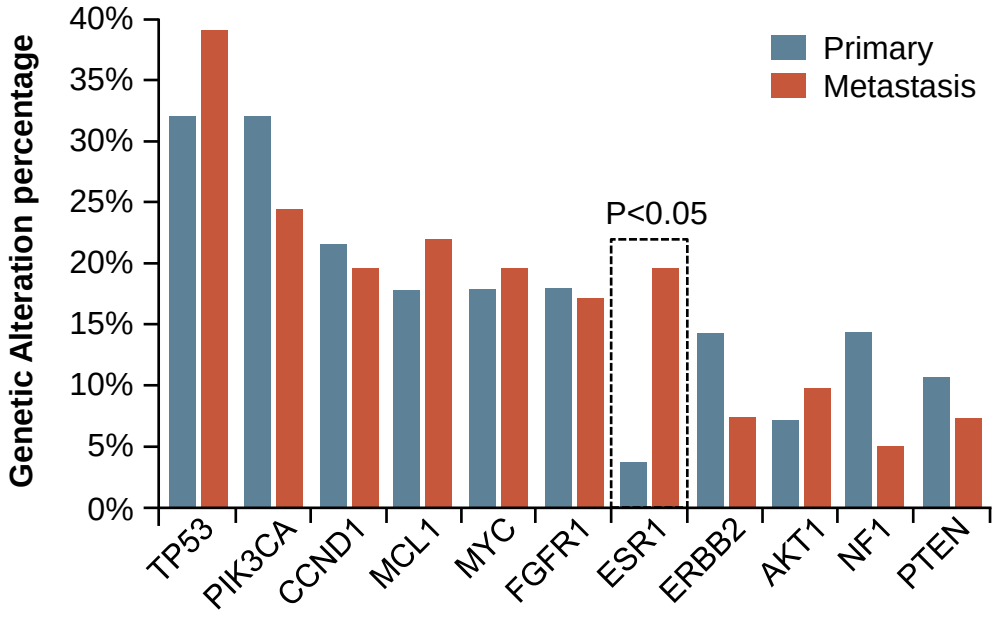
- gBRCA if not performed before
- HER2 Low status (45-60%)
- m*PIK3CA*
- **m*ESR1***
- HER2 mutations (lobular) (sensitivity to TKIs, T-DXd...)
- NTRK gene fusion, rare in luminal BC
- IO biomarkers MSI-h <0.5%, TMB high 10% (lobular)
- No validated biomarkers for CDK4/6i (evidence that basal subtype are resistant)

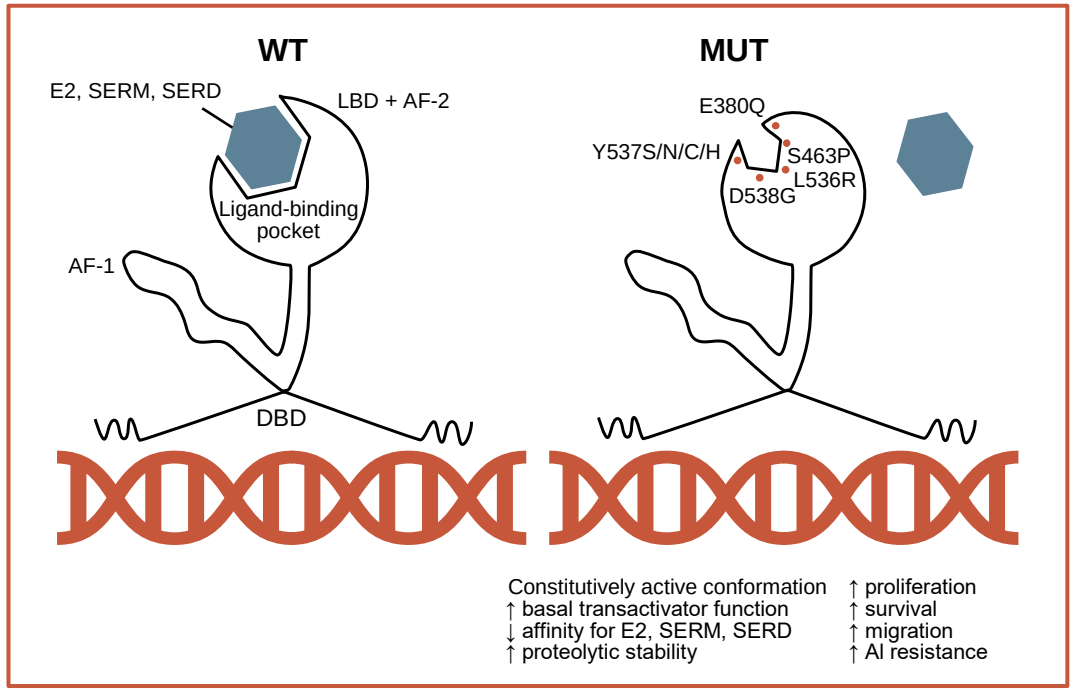
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; gBRCA, germline BReast CAncer gene; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IO, immuno-oncology; mESR1, estrogen receptor 1 mutation; mPIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; NTRK, neurotrophic tyrosine receptor kinase; MSI-h; microsatellite instability High; T-DXd, trastuzumab deruxtecan; TMB, tissue tumour mutational burden; TKI, tyrosine kinase inhibitor

ESR1 MUTATION

ESR1, estrogen receptor 1

ESR1 MUTATION: CLINICAL BIOMARKERS IN HR+ MBC





ESR1 mutation

- 4-5% in recurrent BC after adjuvant AI
- 1.5-7% after neoadjuvant AI
- <1% in MBC not treated by ET
- **20-40% in MBC treated by AI**

AF, activation function; AI, aromatase inhibitor; AKT1, alpha serine/threonine-protein kinase 1; CCND1, cyclin D1; DBD, DNA binding domain; E2, estradiol; ERBB2, v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2; ESR1, estrogen receptor 1; ET, endocrine therapy; FGFR1, fibroblast growth factor receptor 1; HR, hormone receptor; LBD, ligand binding domain; MBC, metastatic breast cancer; MCL1,myeloid cell leukemia-1; MUT, mutant; NF1, neurofibromatosis type 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; TP53, tumour protein 53; WT, wild type

Brett JO, et al. Breast Cancer Res. 2021;23:85; Jeselsohn R, et al. Clin Can Res. 2014;20:1757-67

POLLING QUESTION

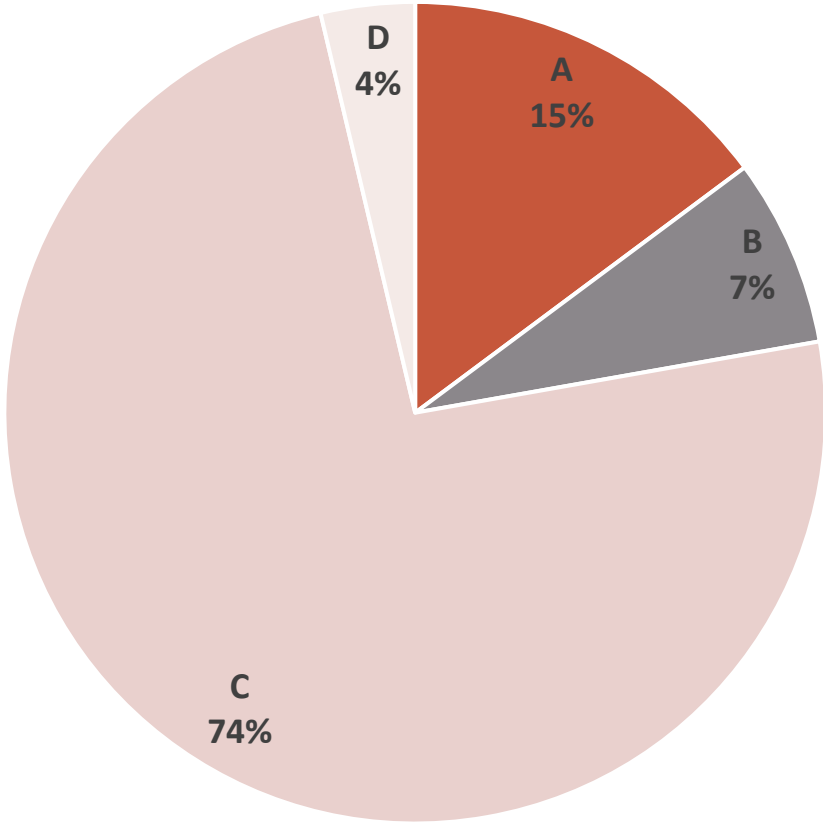
WHAT IS THE MOST COMMON TYPE OF *ESR1* MUTATION IN METASTATIC LUMINAL TUMORS PREVIOUSLY TREATED WITH AI?

A. *ESR1* epigenetic modification

B. *ESR1* amplification

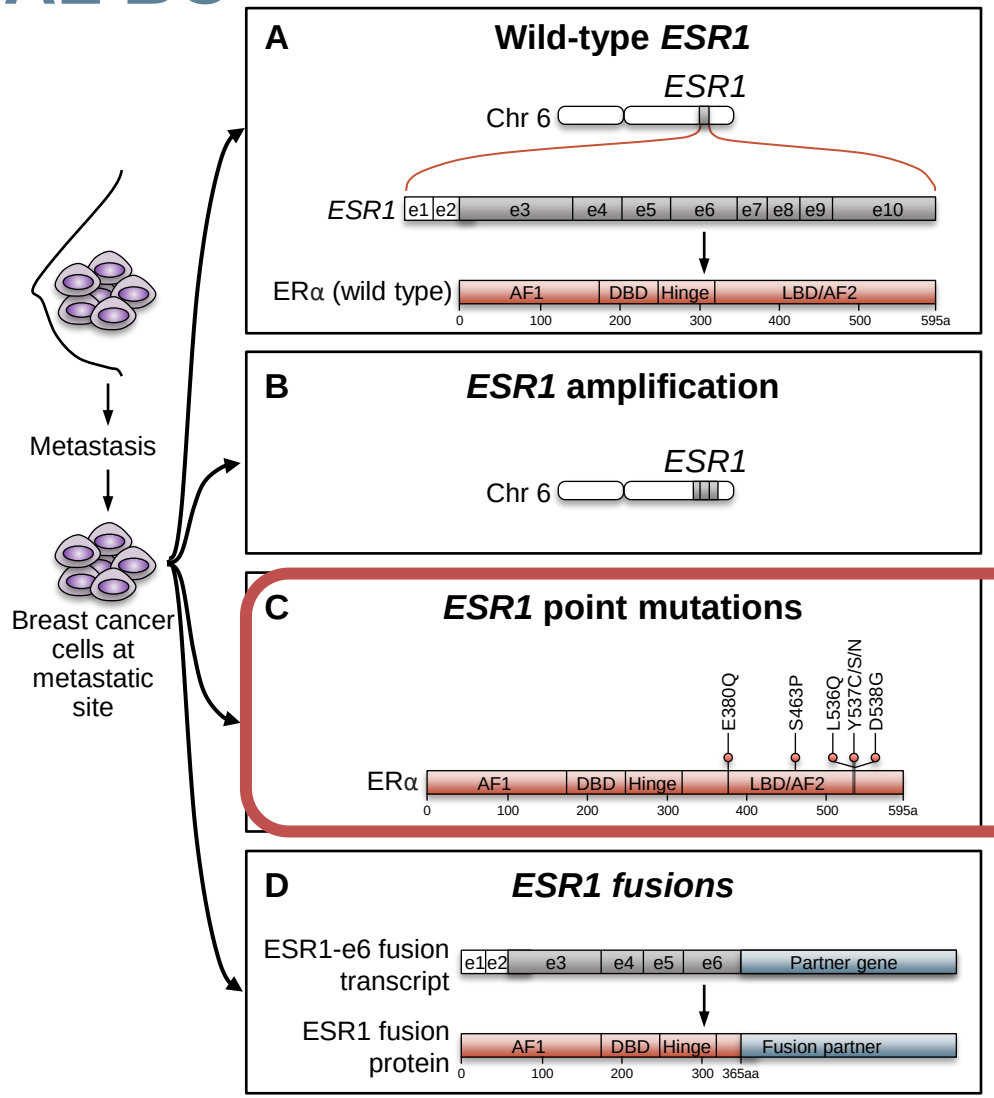
C. *ESR1* point mutation ☑

D. *ESR1* fusion



AI, aromatase inhibitor; ESR1, estrogen receptor 1

DIFFERENT TYPES OF *ESR1* ALTERATIONS IN METASTATIC LUMINAL BC



20% loss of ESR1 expression
(Aurilio et al. Eur J. Cancer 2015)

Epigenetic modifications
Cross Talks

2-20% of luminal tumours
(depending on method)

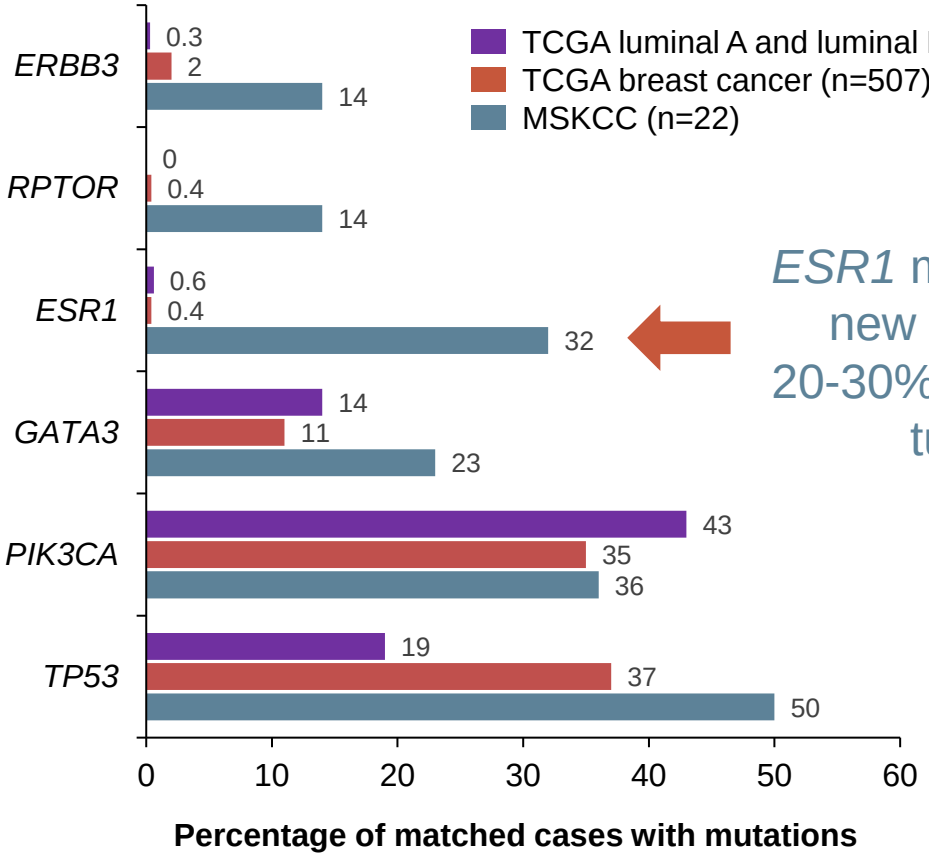
20-30% of metastatic luminal tumours
(<3% of primary tumours)

2-6% of luminal tumours
(different fusion partners)

AF, activation function; BC, breast cancer; Chr, chromosome; DBD, DNA binding domain; e, exons; ERα, estrogen receptor alpha; ESR1, estrogen receptor; LBD, ligand-binding domain

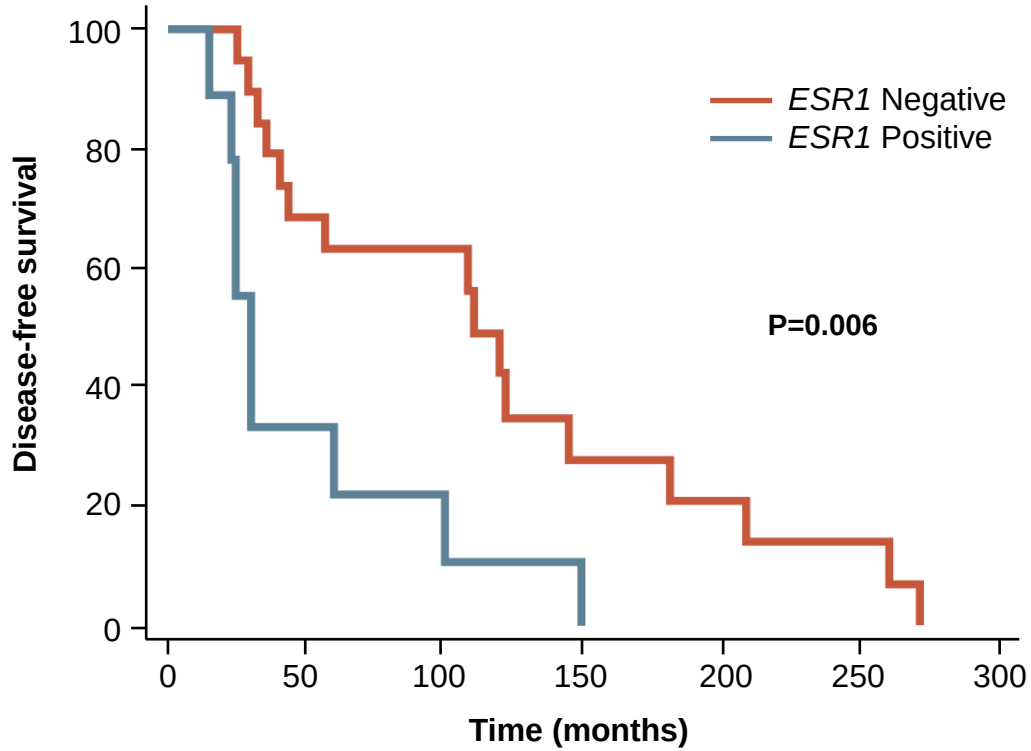
Lei JT, et al. J Cancer Metastasis Treat. 2019;5:38; Nat Com. 2022: 13(1), 2011

ESR1 MUTATIONS: METASTATIC LUMINAL BREAST CANCER



ESR1 mutations as a new mutation in 20-30% of metastatic tumours

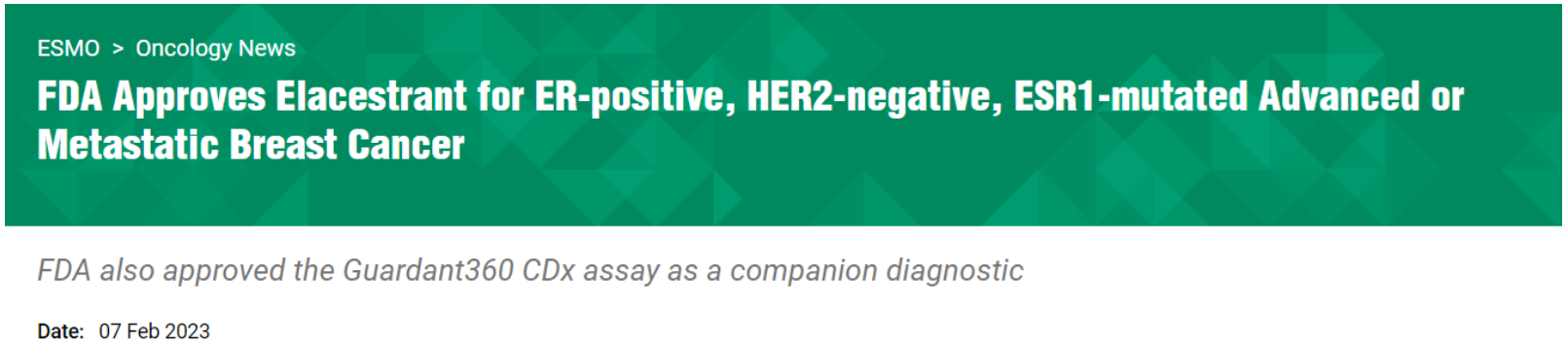
ESR1 mutations are associated with poor outcome



ERBB3,v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog; ESR1, estrogen receptor 1; GATA3, GATA binding protein 3; HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; OS, overall survival; RPTOR, regulatory associated protein of mTOR complex 1; TCGA, The Cancer Genome Atlas; TP53, tumour protein 53; WT, wild type

Toy W, et al. Nat Genet.2013;45:1439-45; Crucitta et al, Cancers 2023:15,1306.; Li Z, et al. Nat Com. 2022: 13(1), 2011

EMERALD TRIAL: BASELINE PATIENT CHARACTERISTICS


ESMO > Oncology News

FDA Approves Elacestrant for ER-positive, HER2-negative, ESR1-mutated Advanced or Metastatic Breast Cancer

FDA also approved the Guardant360 CDx assay as a companion diagnostic

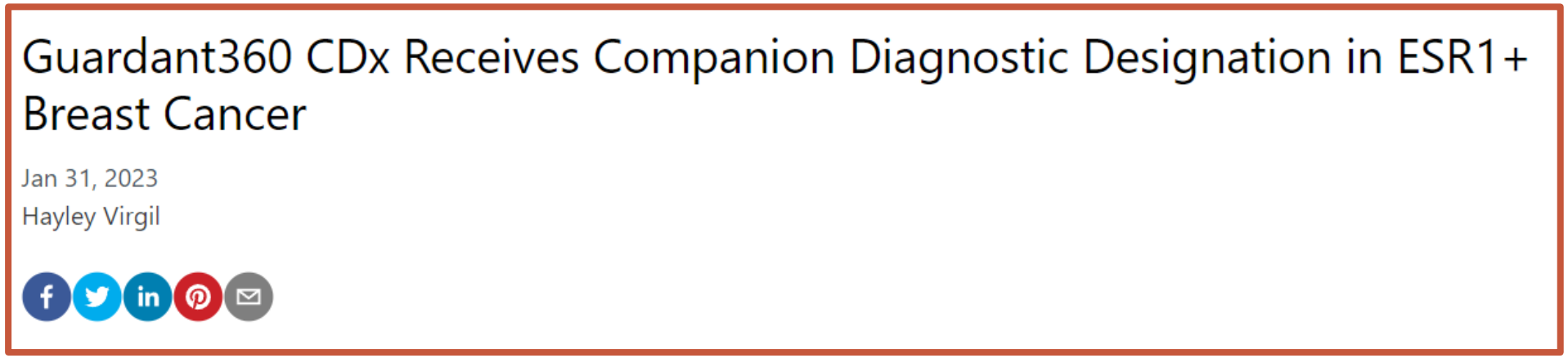
Date: 07 Feb 2023

- Median age was 63 years (range: 24-89)
- **47.8% had a detectable *ESR1* mutation**
- 43.4% had previously received two lines of endocrine therapy for advanced or metastatic disease
- 22.2% received a prior line of chemotherapy for advanced/metastatic disease
- 68.2% had visceral metastases in the elacestrant group
- 71% had visceral metastases in the SoC group
- Guardant360 CDx assay, FDA approved as companion test for ESR1m screening

CDx, companion diagnostics; ER, estrogen receptor; ESR1, estrogen receptor 1; FDA, Food and Drug Administration; HER2, human epidermal factor receptor 2; SoC, standard of care

Bidard FC, et al. J Clin Oncol. 2022.40:3246-56

ESR1 MUTATION: COMPANION DIAGNOSTIC


Guardant360 CDx Receives Companion Diagnostic Designation in ESR1+ Breast Cancer

Jan 31, 2023

Hayley Virgil

The analytical sensitivity of the Guardant360® test at the panel level is

- **100%** with an **allelic fraction >0.5%**
- 88.3% **with an allelic fraction between 0.01-0.5%** for SNVs, based on a cell-free DNA contribution of ≥30 ng in patient samples

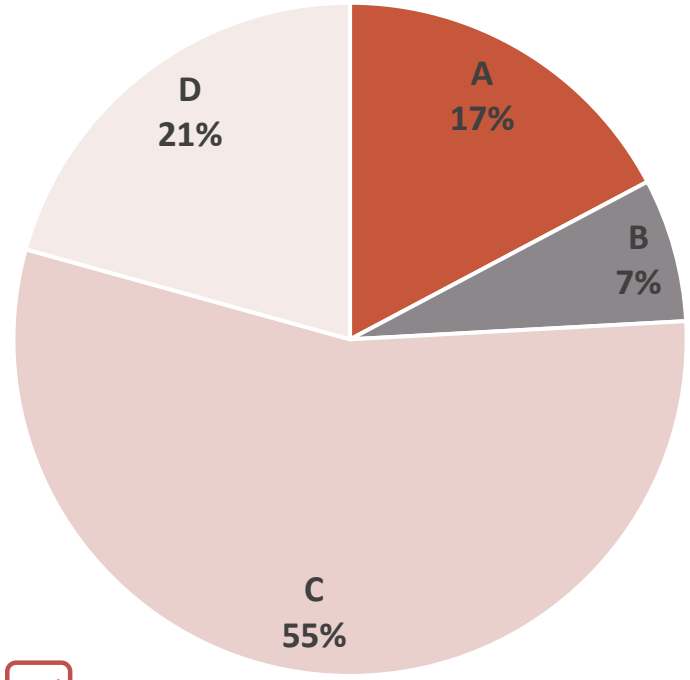
CDx, companion diagnostics; ESR1, estrogen receptor 1; SNV, single nucleotide variant

https://guardanthealth.eu/wp-content/uploads/2021/01/G360-Specification-Sheet-1.pdf (accessed May 22, 2023)

RECOMMENDATIONS & GUIDELINES

POLLING QUESTION

WHEN WOULD YOU TEST FOR *ESR1* MUTATION?



A. Upon diagnosis

B. After 1st line of endocrine therapy only

C. At recurrence or progression on endocrine therapy ☑

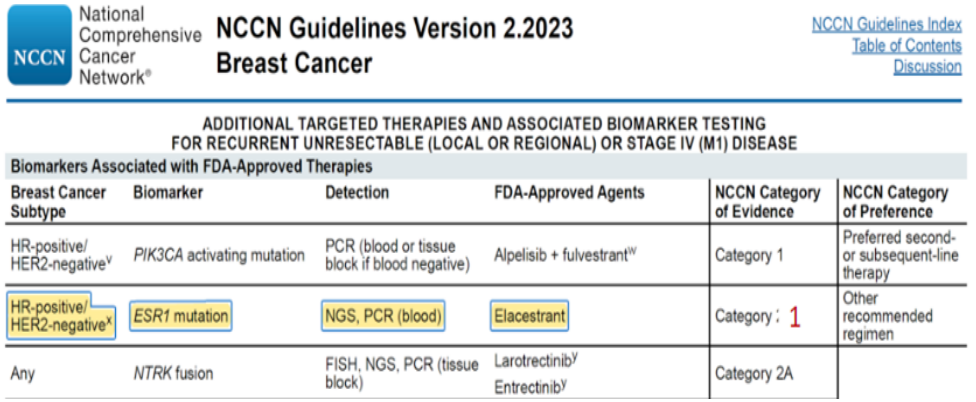
D. All of the above

ESR1, estrogen receptor 1

ESR1 MUTATION: TESTING RECOMMENDATIONS

- When?
  - ASCO 2023 guidelines recommend testing at recurrence or progression on ET (given with or without CDK4/6i)[1]

- How?
  - Liquid biopsy
    - ESMO recommends test in ctDNA
    - ASCO recommends blood-based ctDNA[1]
    - PADA-1 trial used ddPCR
    - NCCN recommends NGS or PCR(blood)[2]



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[x]	*ESR1* mutation	NGS, PCR (blood)	Elacestrant	Category 1	Other recommended regimen
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[y] Entrectinib[y]	Category 2A	

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20*]

ASCO rapid recommen

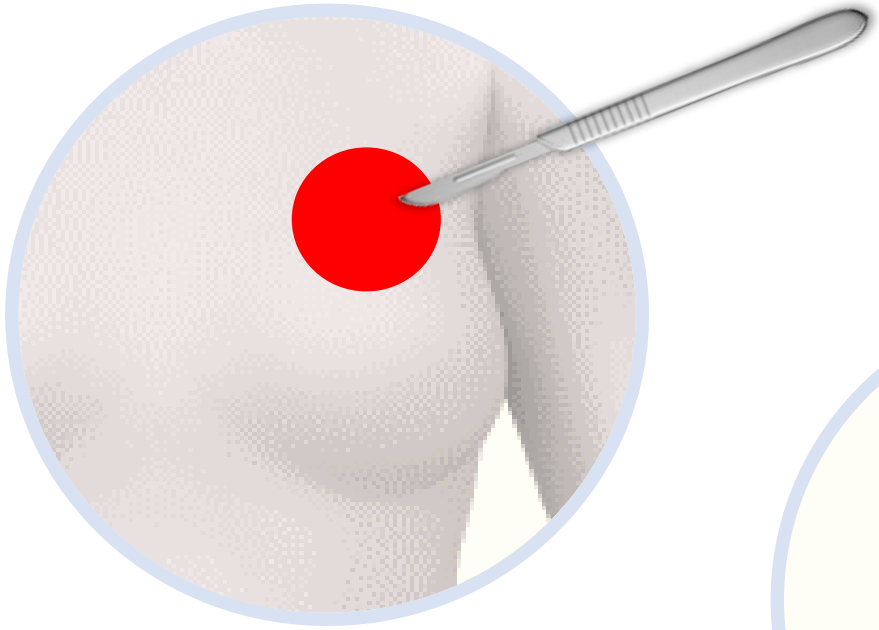
Testing for *ESR1* Mutations to Guide Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update

Harold J. Burstein, MD, PhD[1]; Angela DeMichele, MD[2]; Mark R. Somerfield, PhD[3]; and N. Lynn Henry, MD, PhD[4]; for the Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels

1L, first line treatment; ctDNA, circulating tumour DNA; ESMO; European Society for Medical Oncology; ESR1, estrogen receptor 1; ET, endocrine therapy; (dd) PCR, droplet digital polymerase chain reaction; NCCN, National Comprehensive Cancer Network; NGS, next generation sequencing

[1]https://ascopubs.org/doi/full/10.1200/JCO.23.00638?role=tab&utm_source=twitter&utm_medium=social&utm_content=7656ec54-2b3b-47a0-9520-5eb98fb2df9f&utm_campaign=Twitter+Website+Traffic (accessed May 22, 2023) ; [2]https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf (accessed May 22, 2023)

TISSUE OR PLASMA?



Tissue biopsy

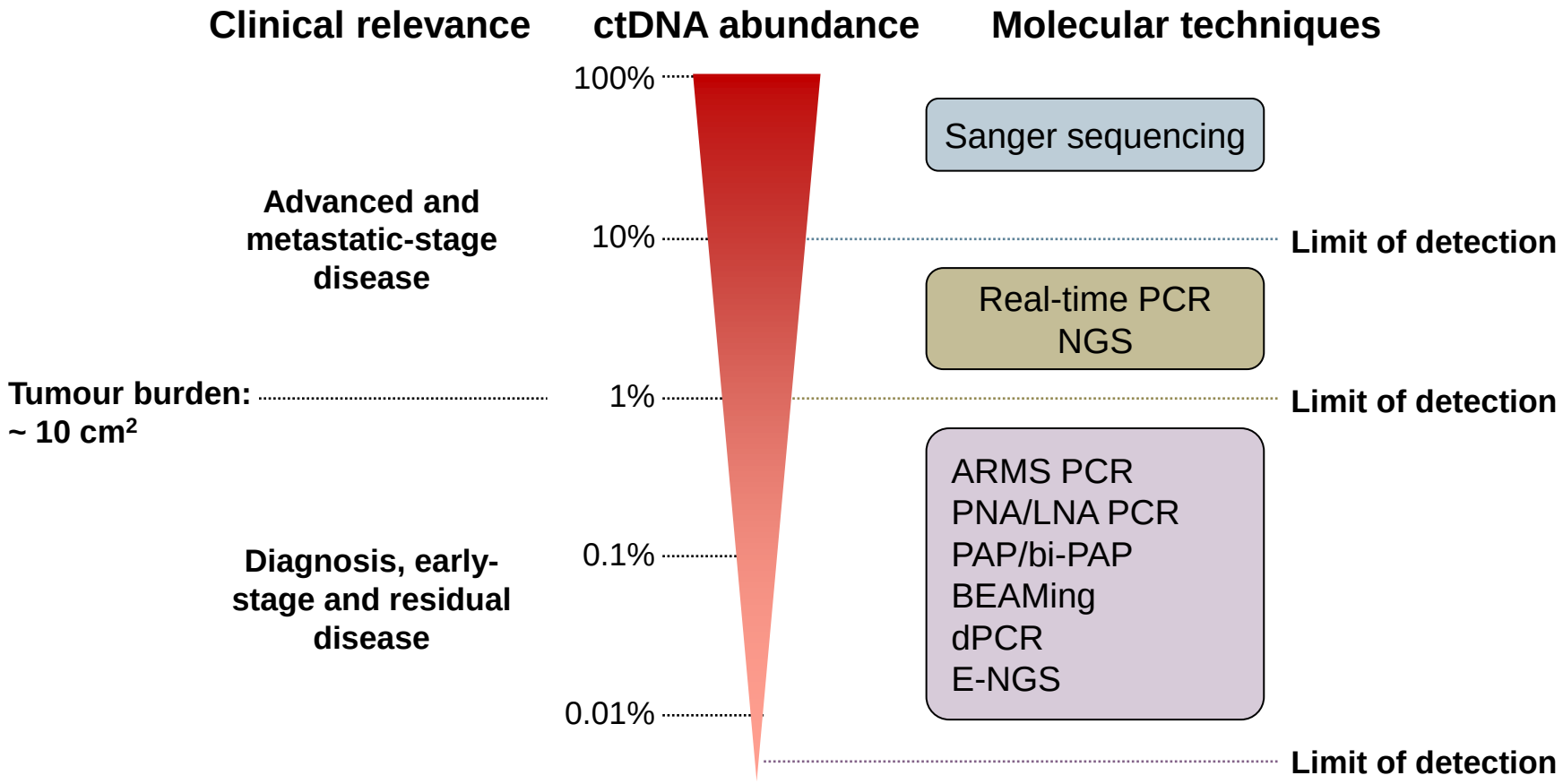
Liquid biopsy

If negative, how long will it take to retest? Or wait for evolution under 2L?

- Little invasive and dynamic
- Captures tissue heterogeneity
- Requires a sensitive technique
- In case of negativity repeat the technique a few months later (limit of sensitivity)

2L, second line of treatment

DETECTION OF CIRCULATING DNA AND AVAILABLE TECHNOLOGIES



ARMS, amplification refractory mutation system; BEAMing, beads, emulsion, amplification, magnetics; bi-PAP, bi-directional pyrophosphorolysis-activated polymerisation; ctDNA, circulating tumour DNA; (d)PCR, (digital) polymerase chain reaction; E-NGS, enhanced next generation sequencing; LNA, locked nucleic acid; PNA; peptide nucleic acid

Saliou A, et al. Expert Rev Mol Diagn. 2016;16:39-50

CIRCUITS TO SEARCH FOR *ESR1* LIQUID BIOPSY MUTATION

Laboratory of biology

<6h

EDTA tubes

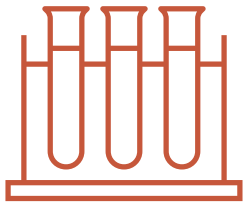
Request for *ESR1* mutation research by oncologist on liquid biopsy **edition of an order form**

Streck tubes

Centrifugation +/– Freezing if not processed on site

Mailing within a week

Return of results 2-15 days



Special shipment **on dry ice bed by carrier**

Molecular Biology Platform:

- DNA extraction
- PCR, ddPCR or NGS technique

EDTA, ethylenediaminetetraacetic acid; ESR1, estrogen receptor 1; (dd)PCR, (droplet digital) polymerase chain reaction; NGS, next generation sequencing; PCR, polymerase chain reaction

CIRCUITS TO SEARCH FOR *ESR1* MUTATION

UNLIKELY BECAUSE RESEARCH TO BE DONE AFTER CDK4/6 FAILURE IS DEBATABLE IF tBRCA

Request for *ESR1* mutation research by oncologist, **edition of an order form**

Pathology structure

2-5 days

Fast postal delivery

Department of Biopathology

- Confirmation of metastasis
- Selection of the tumour area
- Cellularity on H&E

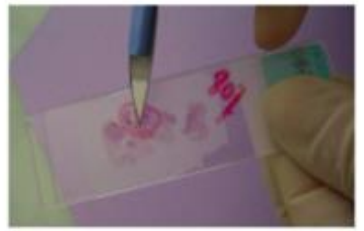
1 day

Scraping the block

Molecular Biology Platform:
- DNA extraction
- PCR, or NGS technique

2 to 15 days

Or chips of tumour



Scraping on blade

CDK4/6, cyclin-dependent kinase 4/6; ESR1, estrogen receptor 1; H&E, hematein & eosin stained slides; NGS, next generation sequencing; PCR, polymerase chain reaction; tBRCA, tumour BReast CAncer gene

CONCLUSION

ESR1 MUTATION: THE NEED FOR & ROLE OF TESTING IN ER+/HER2- METASTATIC BREAST CANCER

- Alterations in ESR1 are mainly in the ligand binding domain and their frequency increases during the course of disease in ER+/HER2- advanced and metastatic breast cancer treated by AI
- Point mutation (25%-40%) > rearrangement (5%) > amplification (1%)
- The presence of *ESR1* mutation seems to be both prognostic (worse) and predictive (resistance to aromatase inhibitors and sensitivity to some SERDs)
- Mutation search is possible without repeated biopsy of a metastatic site
- This research can be performed reliably by liquid biopsy at recurrence or progression on or after endocrine therapy

AI, aromatase inhibitor; ER, estrogen receptor; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; SERD, selective estrogen receptor degrader

DISCUSSION

DISCUSSION & QUESTIONS

KEY CLINICAL TAKEAWAYS

- **Elacestrant** is the **1st oral SERD to be FDA approved** (January 2023) for postmenopausal women or adult men with ER+/HER2-, ***ESR1*-mutated** advanced or metastatic breast cancer
  - FDA approved Guardant360 CDx assay as a companion diagnostic device to identify patients with ER+/HER2- advanced or metastatic breast cancer for treatment with elacestrant
- With the aim of redefining **treatment landscapes**, for ER+/HER2- advanced and metastatic breast cancer, several **oral SERDs are in clinical development** both as monotherapy and in combination therapy with other targeted therapies, including CDK4/6i
- ***ESR1*, PI3K, CDK4/6, BRCA, and AKT pathways alterations** can be used as targets to guide **treatment selection** and **sequencing decisions** in ER+/HER2- advanced or metastatic breast cancer
- ***ESR1* mutational status** can be determined without repeated tissue biopsy of a metastatic site, instead it can be done reliably by **liquid biopsy at recurrence or progression on ET**

AKT, alpha serine/threonine kinase; BRCA, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CDx, companion diagnostics; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; PI3K, phosphoinositide 3-kinase; SERD, selective estrogen receptor degrader

FUTURE PERSPECTIVES

- Awaiting the outcomes of phase 3 trials on Oral SERDs: persevERA, SERENA-6, and the EMBER-3 trial investigating giredestrant, camizestrant, and imlunestrant respectively.
- Ongoing clinical trials investigating combination of oral SERDs with targeted therapies including CDK 4/6i and PI3K/AKT/mTOR inhibitors
- Ongoing clinical trials exploring the role of CDK4/6i beyond progression on prior treatment with CDK4/6i
- Further exploration of novel switch strategies based on circulating tumor DNA (ctDNA) has the potential to refine the therapeutic paradigm in the setting of metastatic breast cancer

COR2ED

THE HEART OF MEDICAL EDUCATION

For more information visit

BREAST CANCER connect®

POWERED BY COR2ED

Connect on
LinkedIn @BREASTCANCER CONNECT

Watch on
YouTube @COR2ED

Email
info@cor2ed.com

Visit us at
https://cor2ed.com/

Follow us on
Twitter @BreastCaConnect

Heading to the heart of Independent Medical Education since 2012